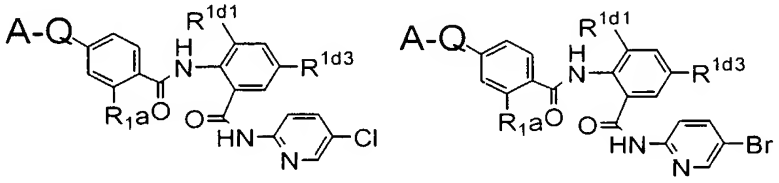
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

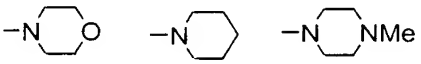
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

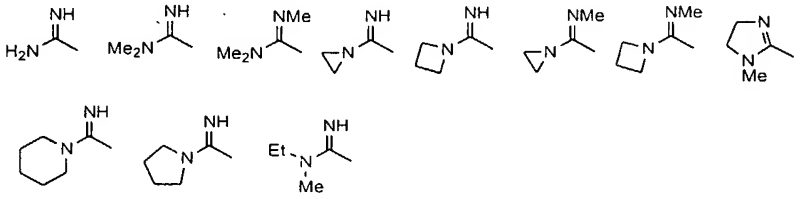
R^{1d1} is selected from H, -OMe, $-NMe_2$,



-N(Me)COOH, -N(Me)COOEt ;

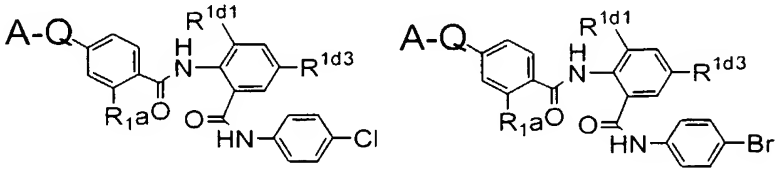
R^{1d3} is Cl or Br;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

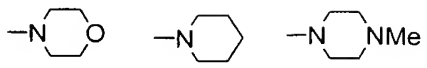
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

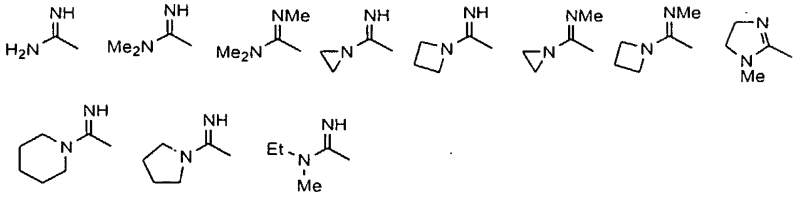
R^{1d1} is selected from H, -OMe, $-NMe_2$,



-N(Me)COOH, -N(Me)COOEt;

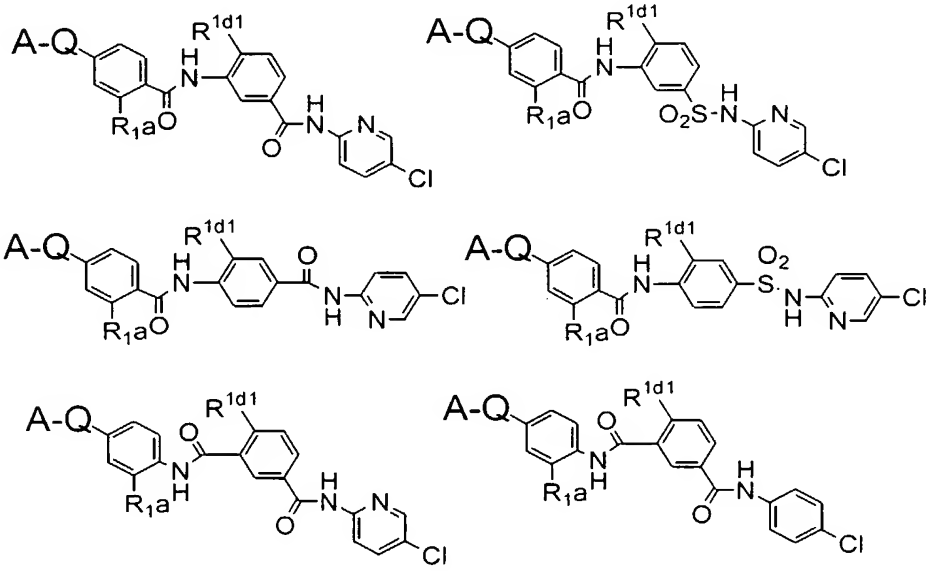
R^{1d3} is Cl or Br;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

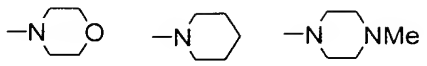
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

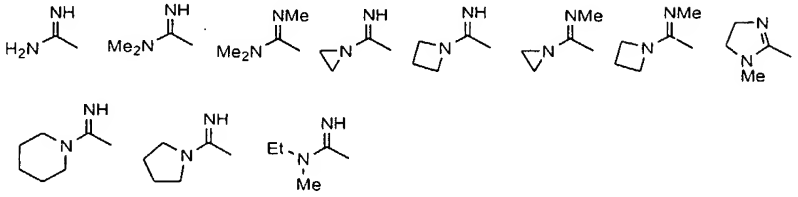
R^{1a} is H or F;

R^{1d1} is selected from H, -OMe, $-NMe_2$,



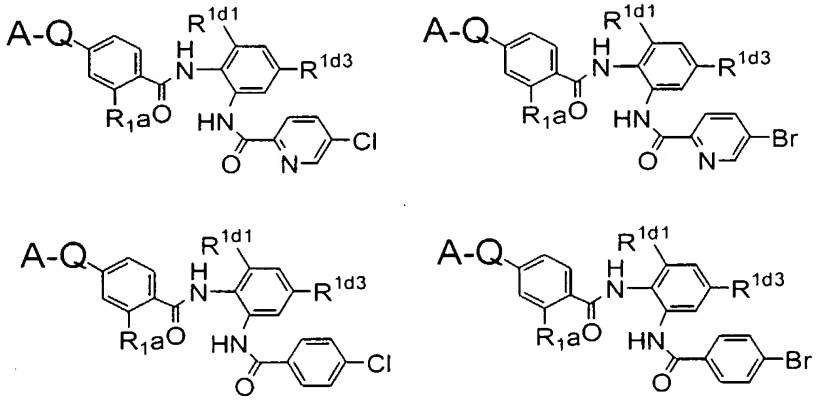
-N(Me)COOH, -N(Me)COOEt;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

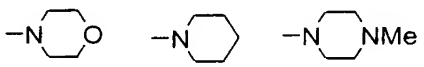
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

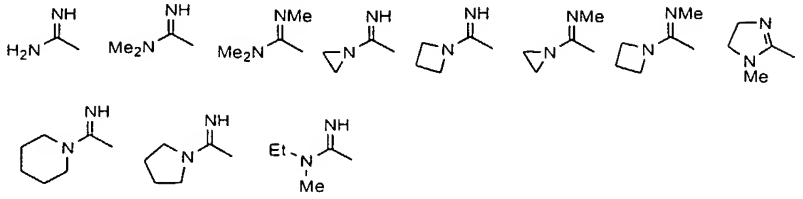
R^{1d1} is selected from H, -OMe, $-NMe_2$,



-N(Me)COOH, -N(Me)COOEt;

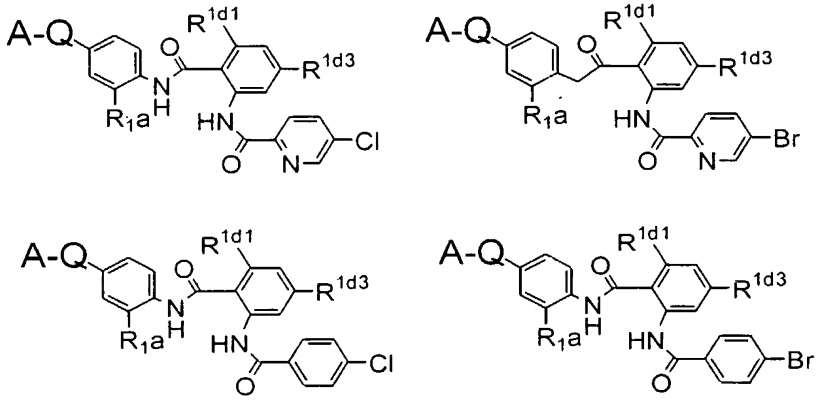
R^{1d3} is -Cl or -Br,

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

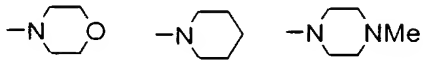
The invention provides a compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

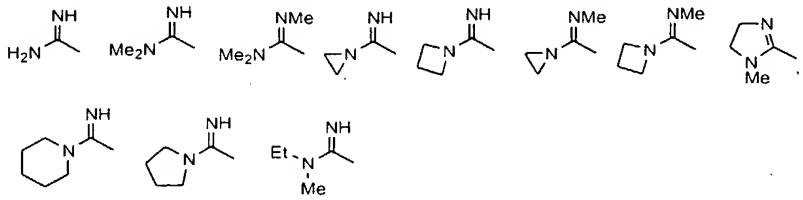
R^{1d1} is selected from H, -OMe, $-NMe_2$,



-N(Me)COOH, -N(Me)COOEt ; and

R^{1d3} is -Cl or -Br,

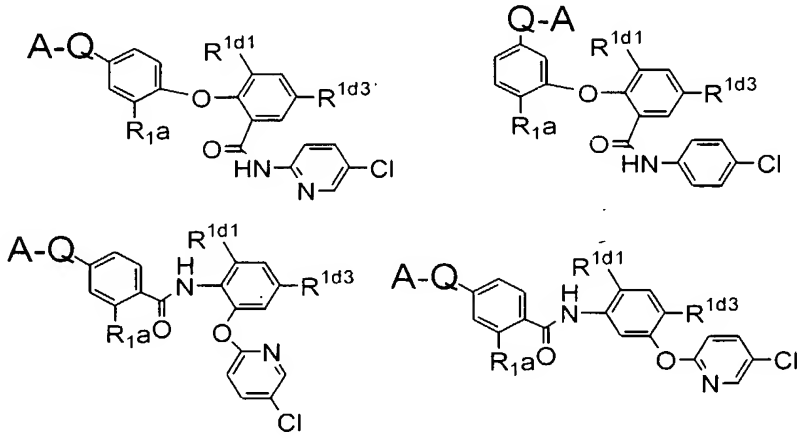
A-Q is a member selected from the group consisting of:



,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

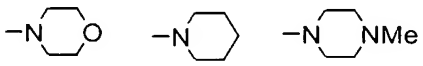
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

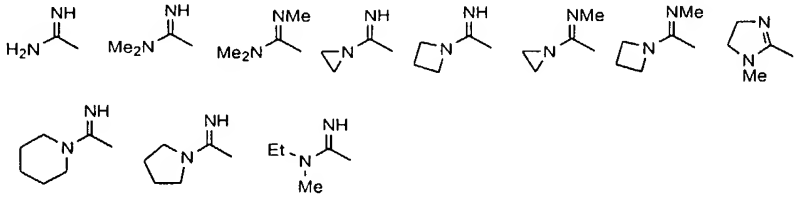
R^{1d1} is selected from H, -OMe, $-NMe_2$,



-N(Me)COOH, -N(Me)COOEt ; and

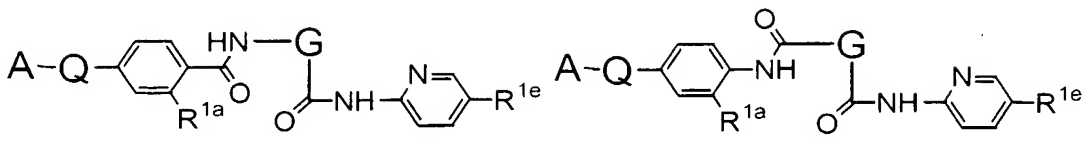
R^{1d3} is -Cl or -Br,

A-Q is a member selected from the group consisting of:



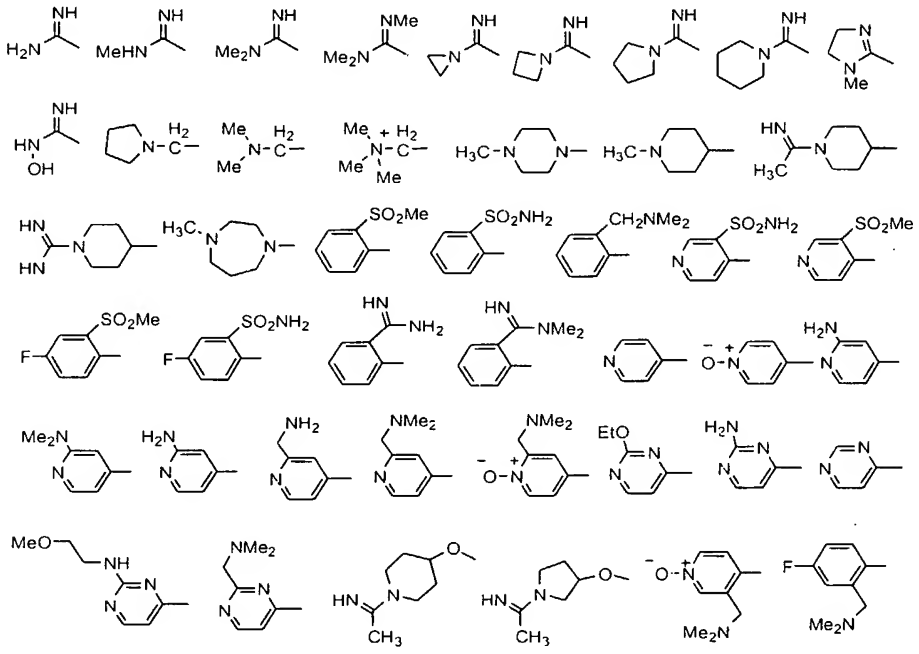
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



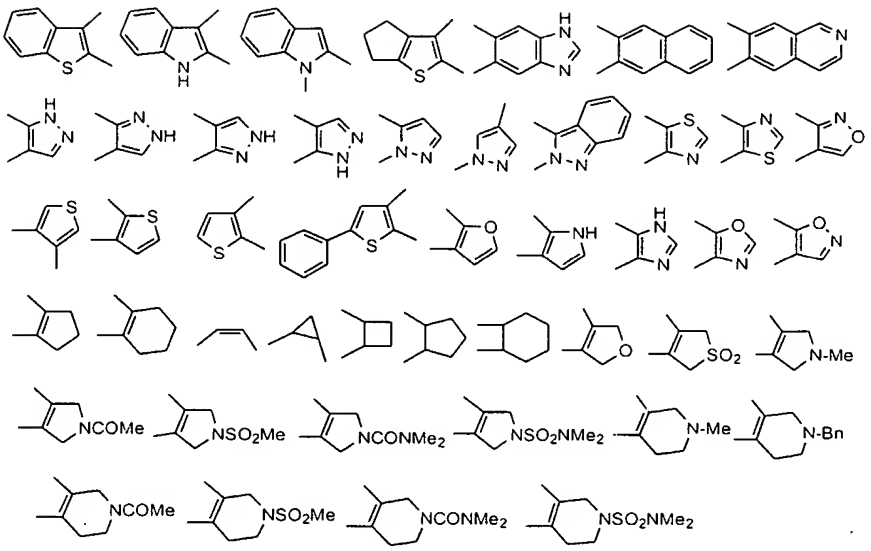
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and Br;

R^{1e} is a member selected from the group consisting of:

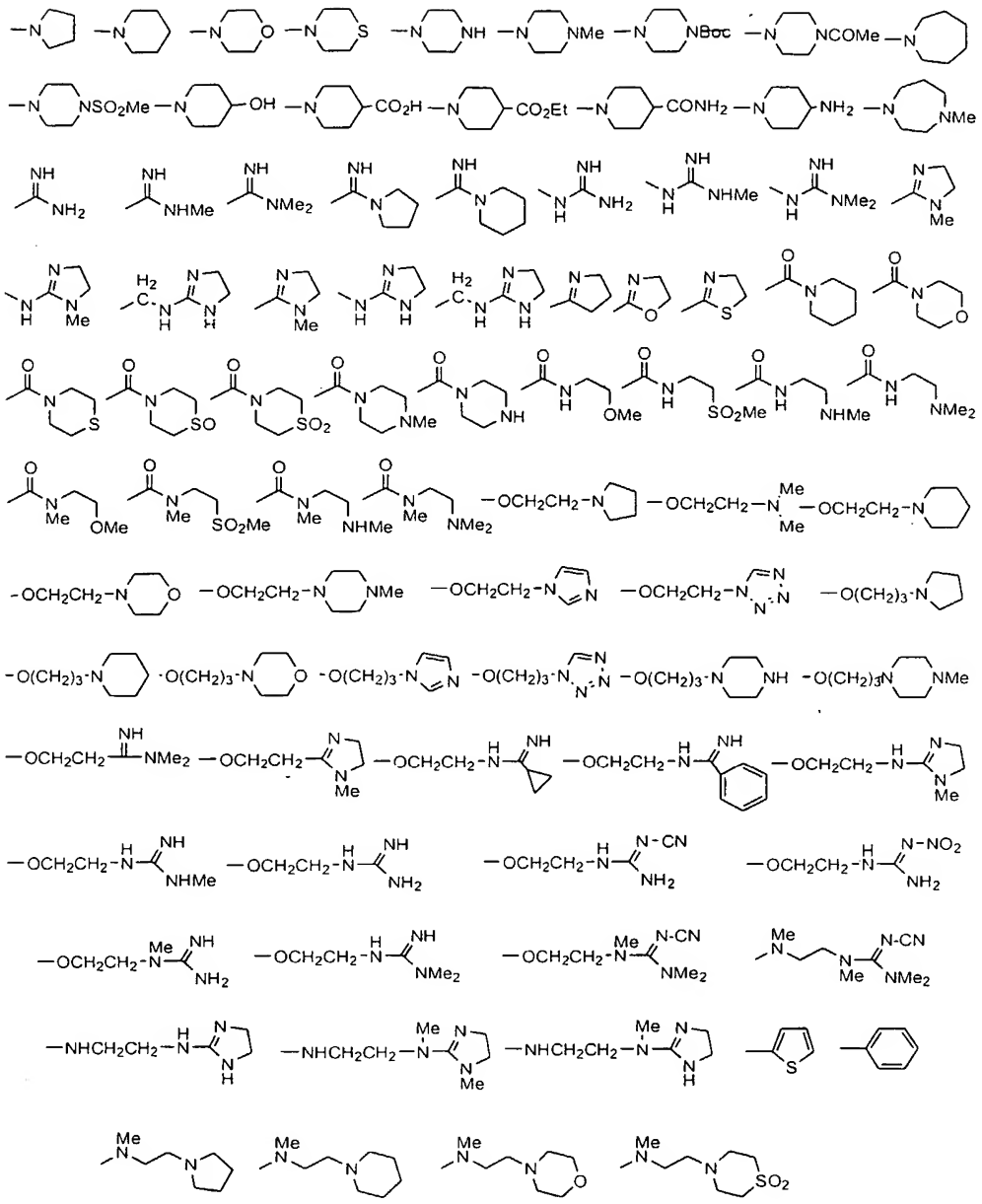
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

G is a member selected from the group consisting of:



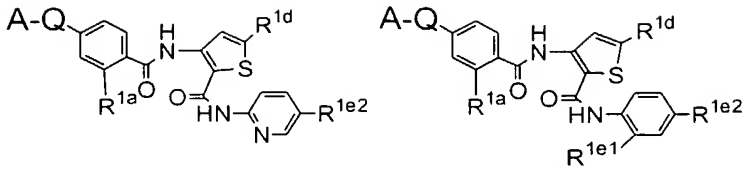
wherein each G group is substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, -Me, -F, -Cl, -Br, aryl, heteroaryl, $-NH_2$, $-NMe_2$, -NHMe, $-NHSO_2Me$, -NHCOMe, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NO_2$, -CN, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CONH_2$, -CONHMe, $-CONMe_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-SO_2NMe_2$, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHMe$, $-CH_2NMe_2$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2CO_2Et$, $-OCH_2CONH_2$, $-OCH_2CONMe_2$, $-OCH_2CONHMe$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-NHCH_2CH_2OMe$, $-SCH_2CH_2OMe$, $-SO_2CH_2CH_2OMe$, $-OCH_2CH_2SO_2Me$, $-NHCH_2CH_2NHMe$, $-NHCH_2CH_2NMe_2$, $-N(CH_2CH_2OH)_2$, $-N(CH_2CH_2OMe)_2$, $-NHCH_2CO_2H$, $-NHCH_2CO_2Et$, $-NHCH_2CO_2Et$, $-NHCH_2CONH_2$, $-NHCH_2CONMe_2$, $-NHCH_2CONHMe$, $-N(CH_3)CH_2CO_2H$, $-N(CH_3)CH_2CO_2Et$, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,



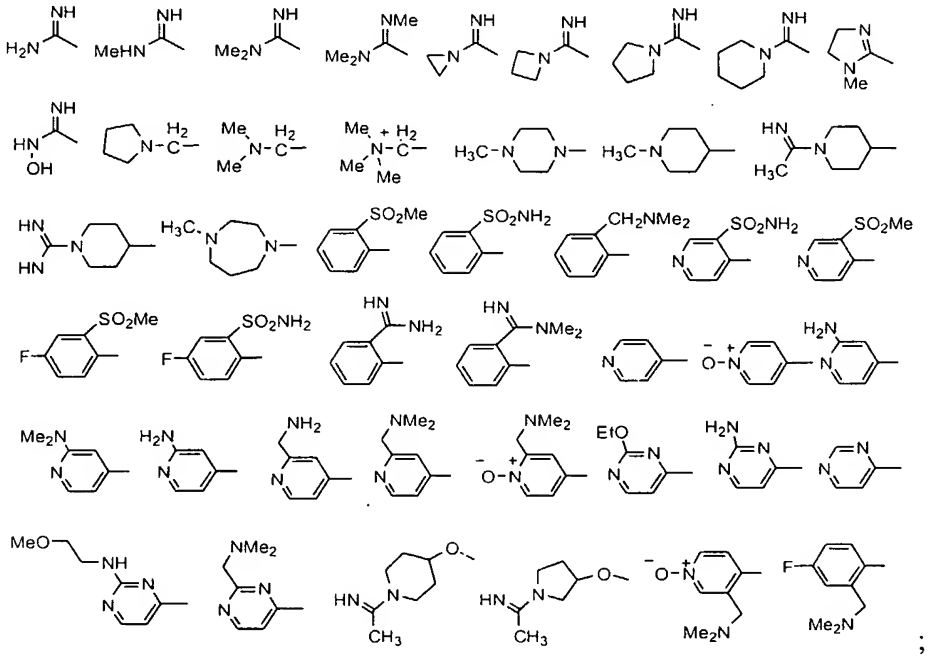
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group of:



;

R^{1a} is a member selected from the group of:

H, -F, -Cl, -Br;

R^{1d} is a member selected from the group of:

H, -F, -Cl, -Br, -OMe;

R^{1e1} is a member selected from the group of:

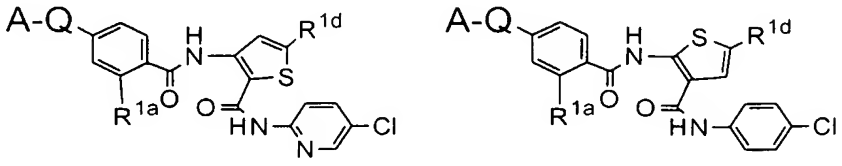
H, -F, -Cl, -Br, $-NH_2$, $-CH_2NH_2$, -OMe, -OH, -CN, $-SO_2Me$, $-SO_2NH_2$; and

R^{1e2} is a member selected from the group of:

H, -F, -Cl, -Br, $-NH_2$,

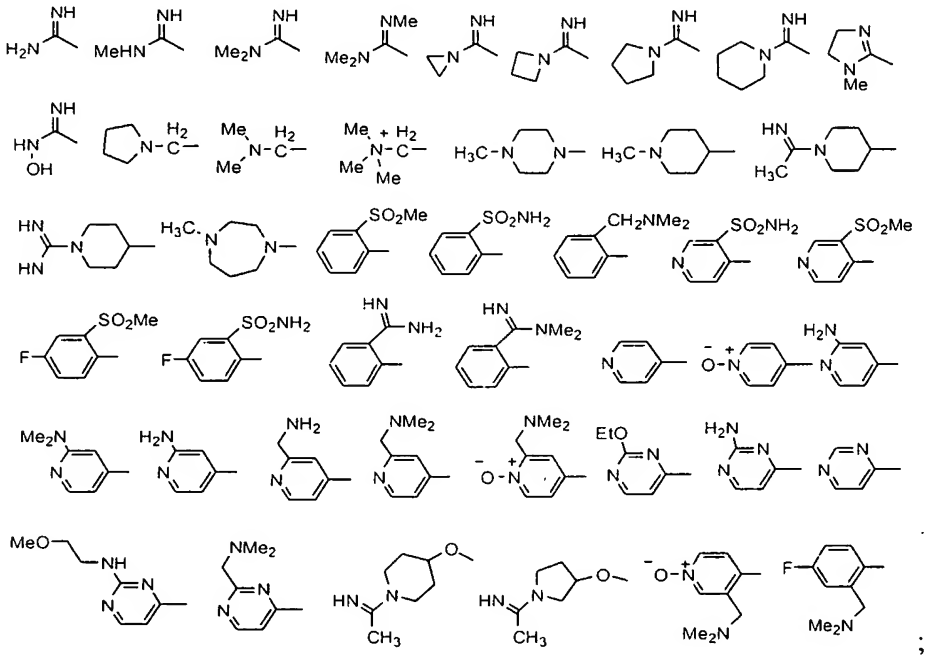
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group of :



;

R^{1a} is a member selected from the group of:

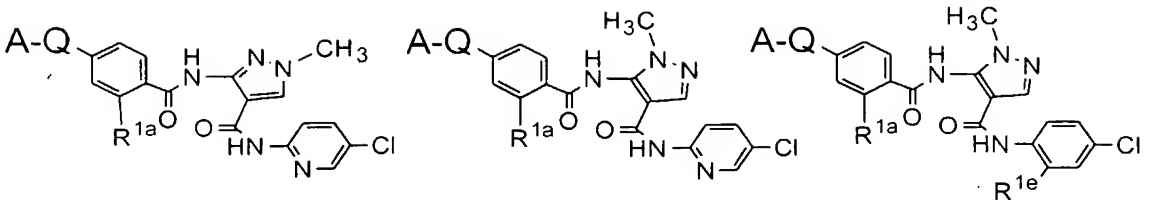
H, -F, -Cl and Br; and

R^{1d} is a member selected from the group of:

H, -F, -Cl, -Br, -OMe,

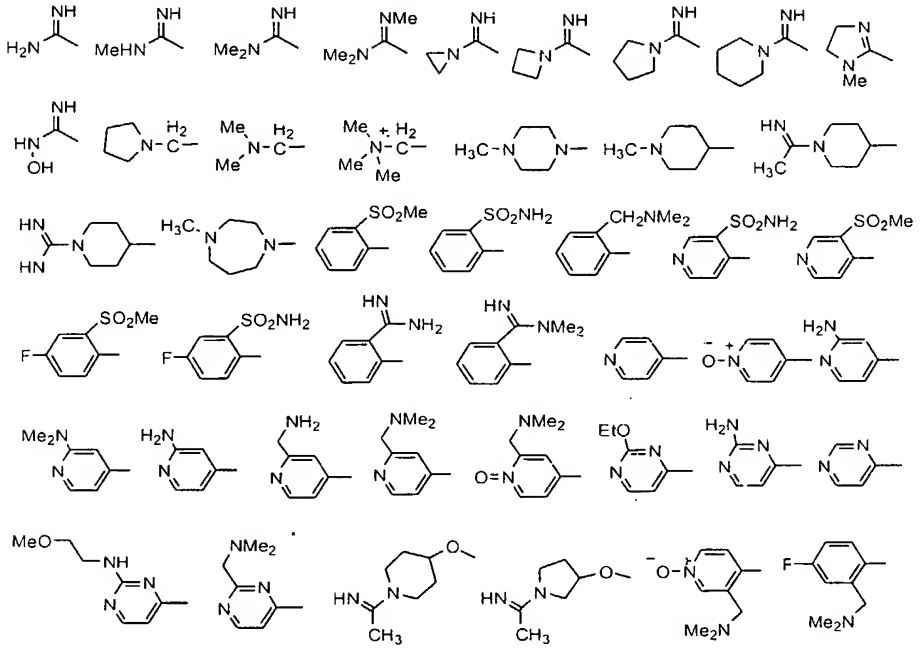
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group of :



;

R^{1a} is a member selected from the group of:

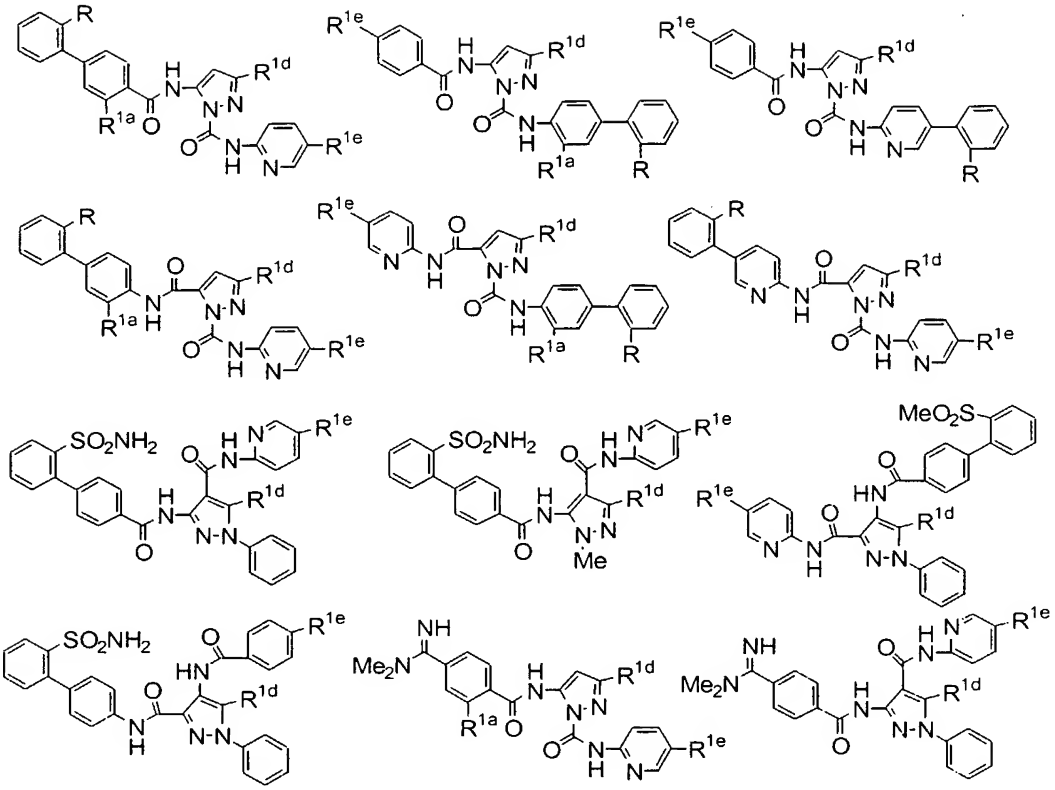
H, -F, -Cl and Br; and

R^{1e} is a member selected from the group of:

H, -F, -Cl, -Br, $-NH_2$, $-CH_2NH_2$, -OMe, -OH, -CN, $-SO_2Me$, $-SO_2NH_2$,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R is a member selected from the group of :

$-SO_2NH_2$, $-SO_2Me$. $-CH_2NMe_2$;

R^{1a} is a member selected from the group of:

H, -F, -Cl, -Br;

R^{1d} is a member selected from the group of:

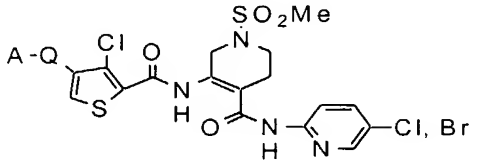
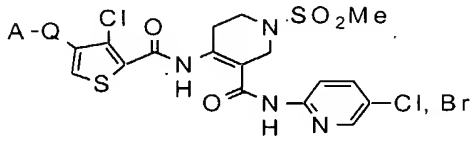
H, -F, -Cl, -Br, -CN, CF_3, $-CH_3$, $-SO_2NH_2$, $-SO_2Me$; and

R^{1e} is a member selected from the group of:

-Cl, -Br,

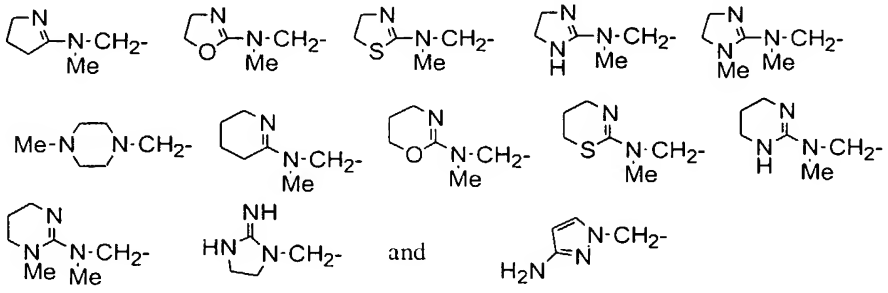
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

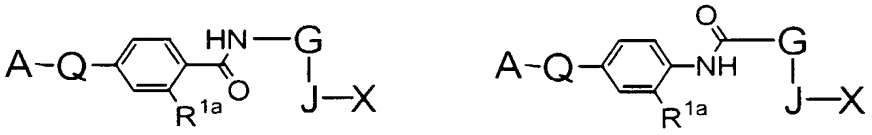
wherein:

A-Q taken together are a member selected from the group consisting of:



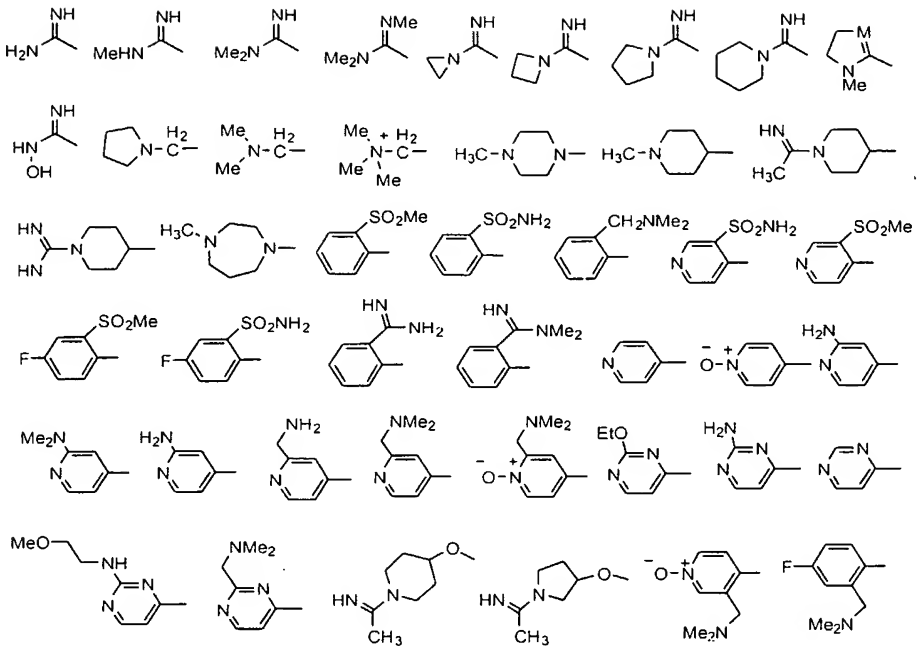
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

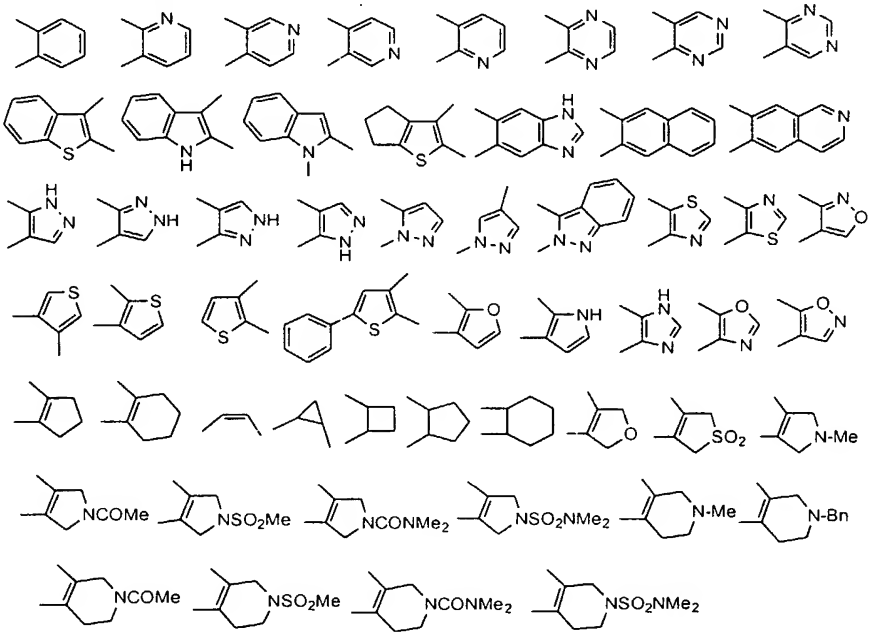
A-Q is a member selected from the group consisting of:



R^{1a} is a member selected from the group consisting of:

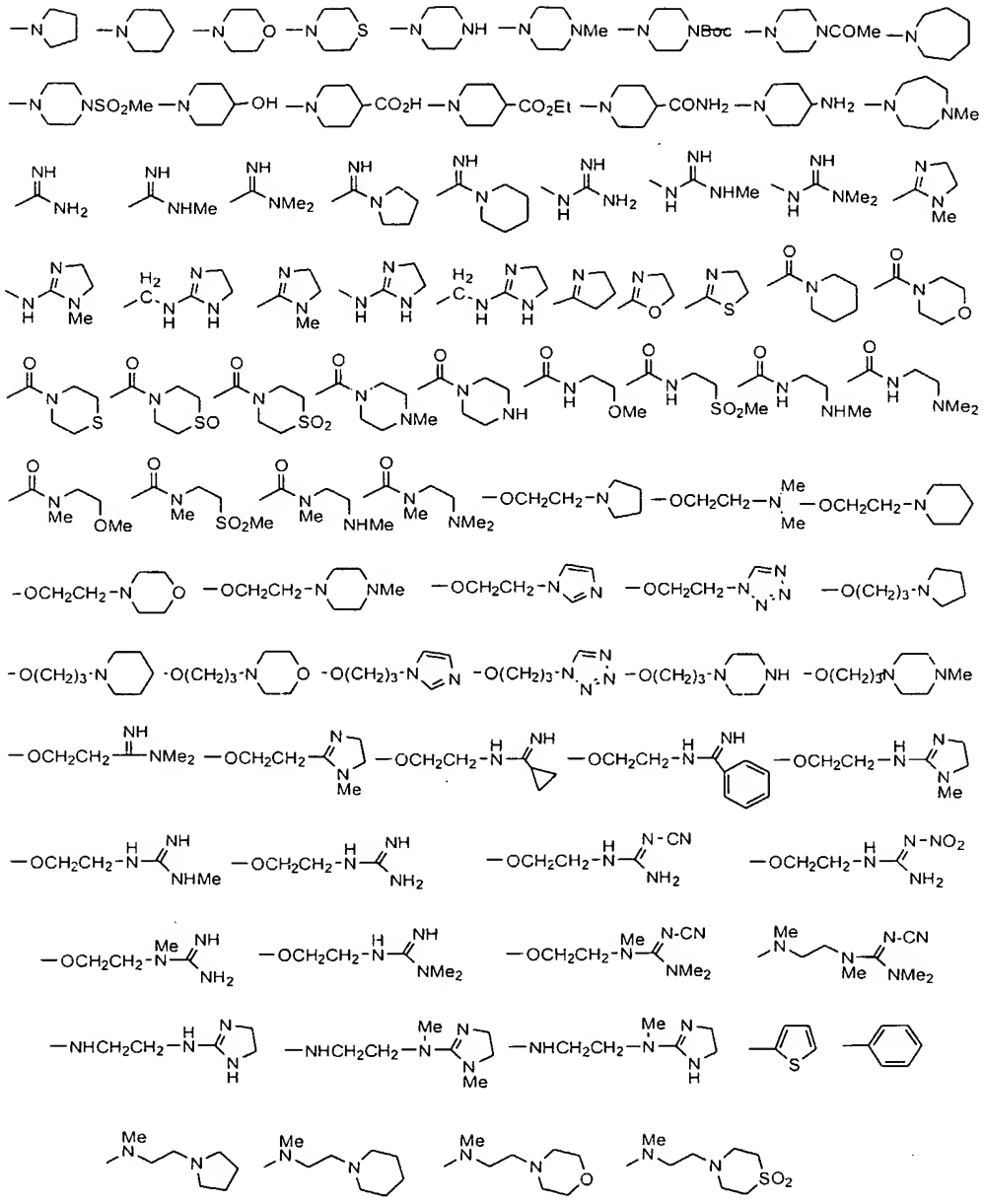
H, -F, -Cl and Br;

G is a member selected from the group consisting of:



wherein each G group is substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, -Me, -F, -Cl, -Br, aryl, heteroaryl, $-NH_2$, $-NMe_2$, -NHMe, $-NHSO_2Me$, -NHCOMe, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NO_2$, -CN, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CONH_2$, -CONHMe, $-CONMe_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-SO_2NMe_2$, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHMe$, $-CH_2NMe_2$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2CO_2Et$, $-OCH_2CONH_2$, $-OCH_2CONMe_2$, $-OCH_2CONHMe$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-NHCH_2CH_2OMe$, $-SCH_2CH_2OMe$, $-SO_2CH_2CH_2OMe$, $-OCH_2CH_2SO_2Me$, $-NHCH_2CH_2NHMe$, $-NHCH_2CH_2NMe_2$, $-N(CH_2CH_2OH)_2$, $-N(CH_2CH_2OMe)_2$, $-NHCH_2CO_2H$, $-NHCH_2CO_2Et$, $-NHCH_2CO_2Et$, $-NHCH_2CONH_2$, $-NHCH_2CONMe_2$, $-NHCH_2CONHMe$, $-N(CH_3)CH_2CO_2H$, $-N(CH_3)CH_2CO_2Et$, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,

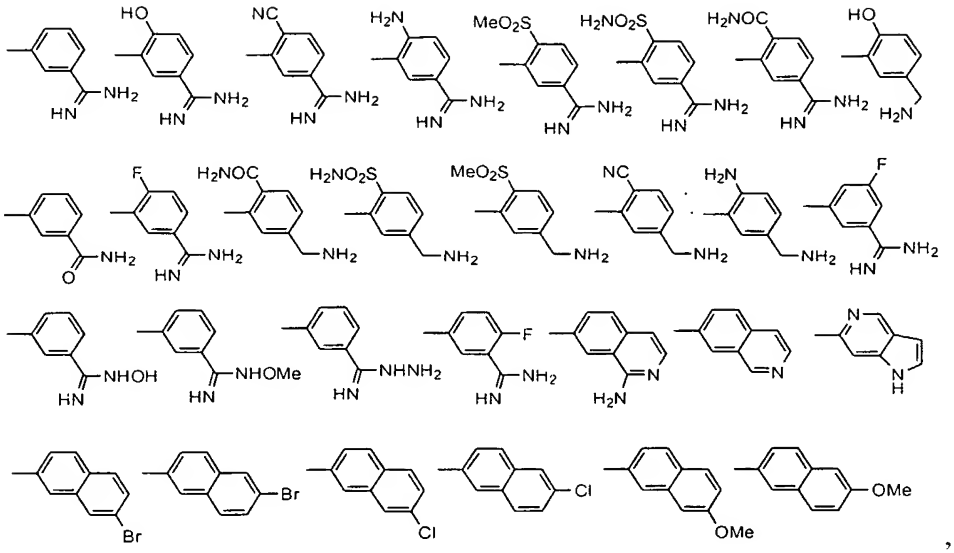


;

J is a member selected from the group consisting of:

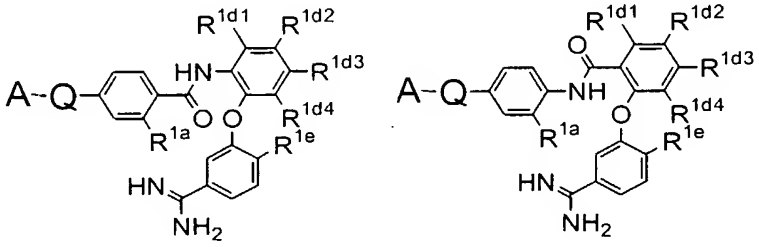
-CONH-, -NHCO-, -O-, -NH-, -NMe-, -CONMe-, -NMeCO-; and

X is a member selected from the group consisting of:



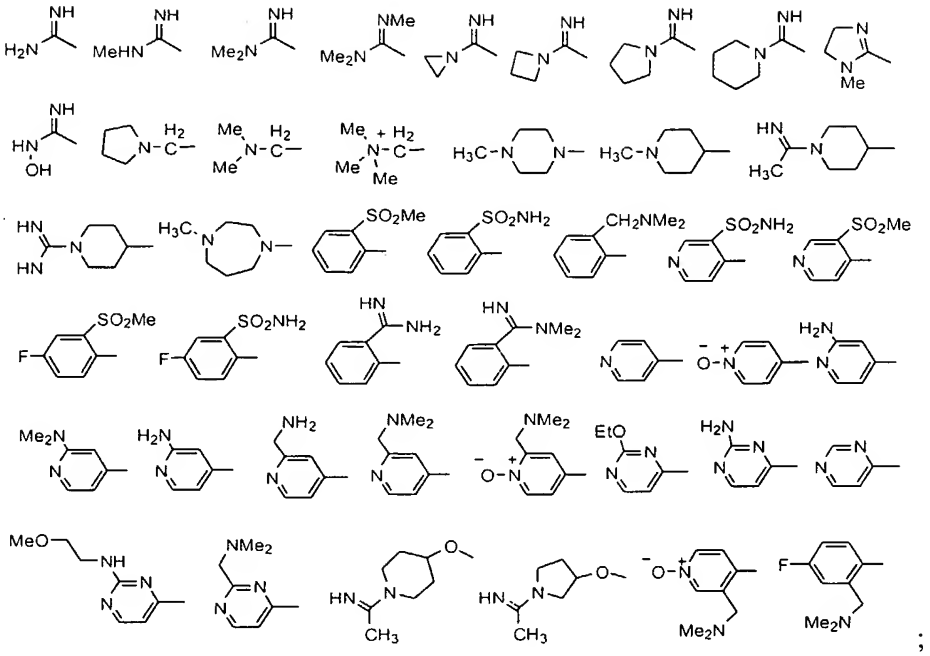
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure :



wherein:

A-Q is a member selected from the group of:



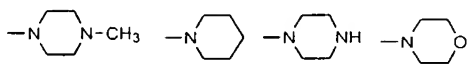
;

R^{1a} is a member selected from the group of:

H, -F, -Cl, -Br;

R^{1d1}, R^{1d2}, R^{1d3} and R^{1d4} is independently a member selected from the group of:

H, -F, -Cl, -Br, -NO_2, -NH_2, -NHMe, -NMe_2, -NHAc, -$NHSO_2Me$, -SO_2Me, -CO_2H, -CO_2Me, -OH, -OMe, -N(Me)CO2H, -N(Me)CO2Et and

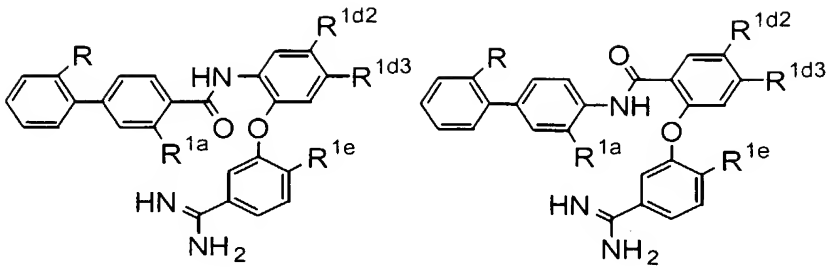

; and

R^{1e} is a member selected from the group of:

H, -OH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



R is a member selected from the group of:

$-SO_2Me$, $-SO_2NH_2$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$;

R^{1a} is a member selected from the group of:

H, -F;

R^{1d2} and R^{1d3} is independently a member selected from the group of:

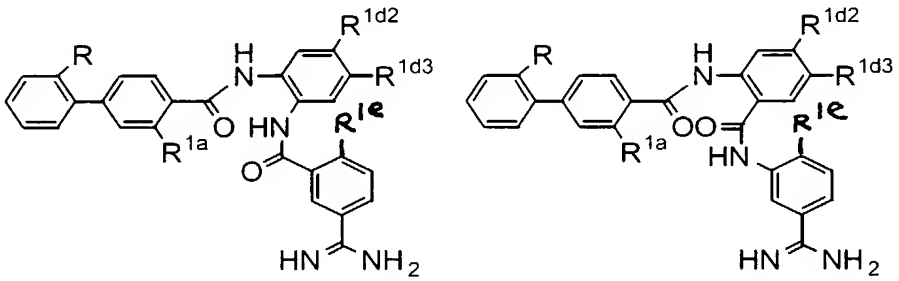
H, -F, -Cl, -Br, $-NO_2$, $-NH_2$, -NHMe, $-NMe_2$, -NHAc, $-NHSO_2Me$, $-SO_2Me$, $-CO_2H$, $-CO_2Me$, -OH, -OMe; and

R^{1e} is a member selected from the group of:

H, -OH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R is a member selected from the group of:

$-SO_2Me$, $-SO_2NH_2$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$;

R^{1a} is a member selected from the group of:

H, -F;

R^{1d2} and R^{1d3} is independently a member selected from the group of:

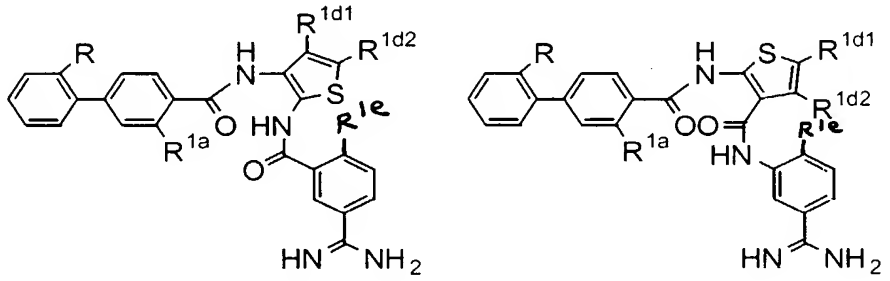
H, -F, -Cl, -Br, $-NO_2$, $-NH_2$, -NHMe, $-NMe_2$, -NHAc, $-NHSO_2Me$, $-SO_2Me$, $-CO_2H$, $-CO_2Me$, -OH, -OMe; and

R^{1e} is a member selected from the group of:

H, -OH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



R is a member selected from the group of:

$-SO_2Me$, $-SO_2NH_2$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$;

R^{1a} is a member selected from the group of:

H, -F;

R^{1d1} and R^{1d2} is independently a member selected from the group of:

H, -F, -Cl, -Br, -OMe; and

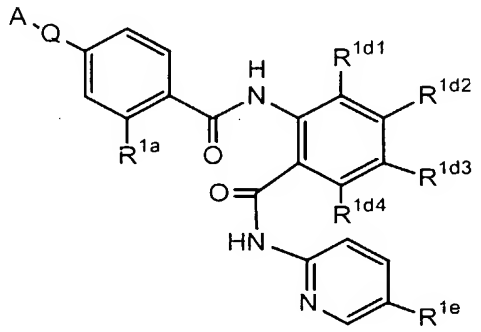
R^{1e} is a member selected from the group of:

H, -OH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The following preferred embodiments of the present invention illustrate compounds wherein the central aromatic ring structure is divalent phenylene, however divalent 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms may be substituted for the bivalent phenylene structure. Further the terminal aromatic ring substituted which is substituted by a R^{1e} group as illustrated below in the preferred embodiments is either a phenyl or a 2-pyridyl group, however other 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms can be substituted for either the phenyl or 2-pyridyl. Moreover, 2 to 3 additional R^{1e} groups other than hydrogen may each be independently substituted for a hydrogen atom attached to a ring carbon on the terminal rings illustrated or substituted for the illustrated terminal ring structure.

A preferred embodiment of the invention provides a compound of formula VIII:



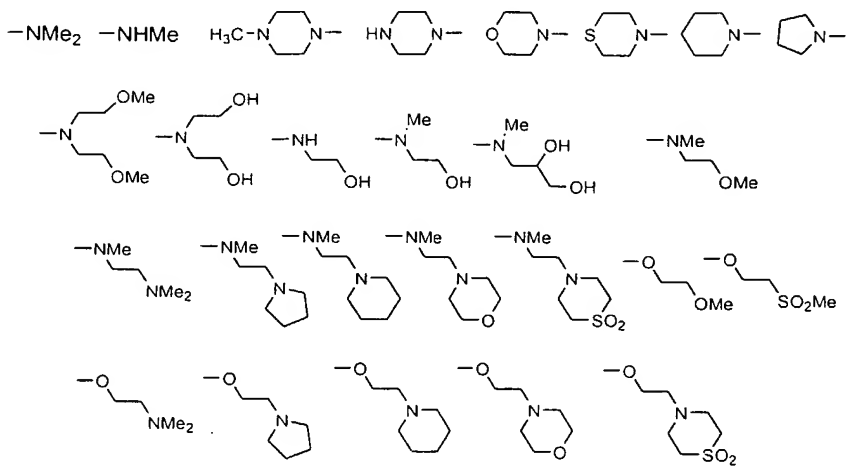
(VIII)

wherein:

R^{1a} is a member selected from the group of H, -F, -Cl and Br;

R^{1d2} and R^{1d4} are each H or F;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H, -Cl, -F, -Br, -OH, -OMe, $-OCF_3$, $OCHF_2$, OCH_2F, $-NH_2$, $-NMe_2$, $-OCH_2COOEt$, $-OCH_2COOH$, - $N(Me)CH_2COOH$, -N(Me)COOEt, and,

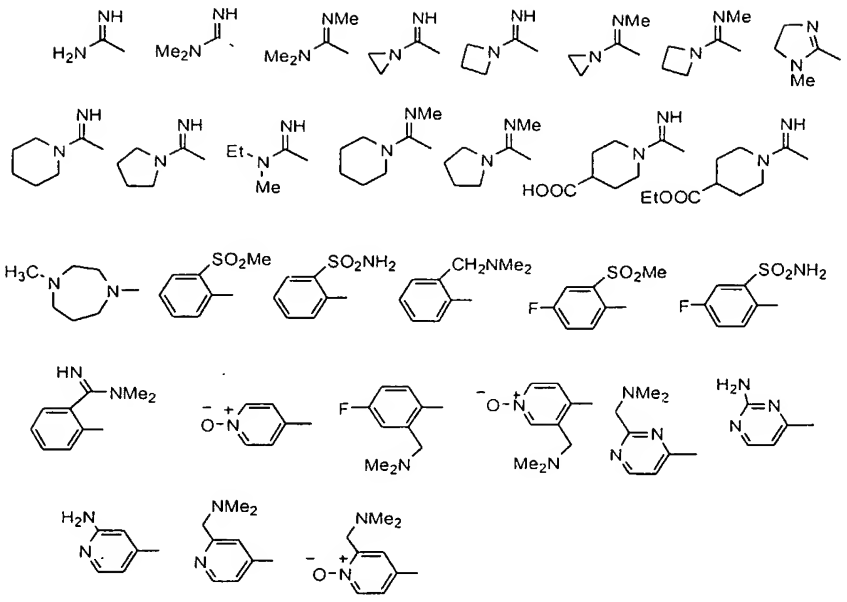


-N(Me)COOEt, -N(Me)CH2OOH,

;

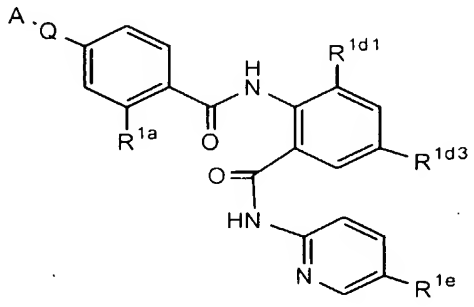
R^{1c} is a member selected from the group of -F, -Cl, -Br, -OH, -Me and -OMe;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

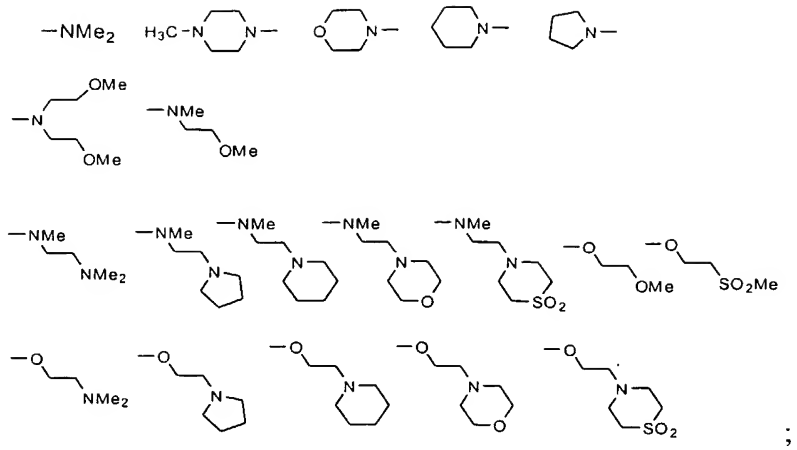
Another preferred embodiment provides a compound of formula VIII having the following structure:



wherein:

R^{1a} is a member selected from the group of H, or -F;

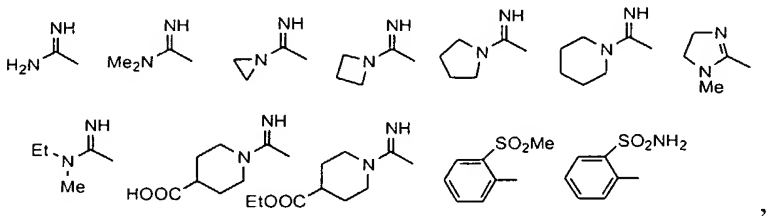
R^{1d1} is each independently a member selected from the group of H, -Cl, -OMe, $-NMe_2$, $-OCH_2COOEt$, $-OCH_2COOH$, - $N(Me)CH_2COOH$, -N(Me)COOEt,



R^{1d3} are independently a member selected from the group of H, -Cl, -Br, -F, and -OMe;

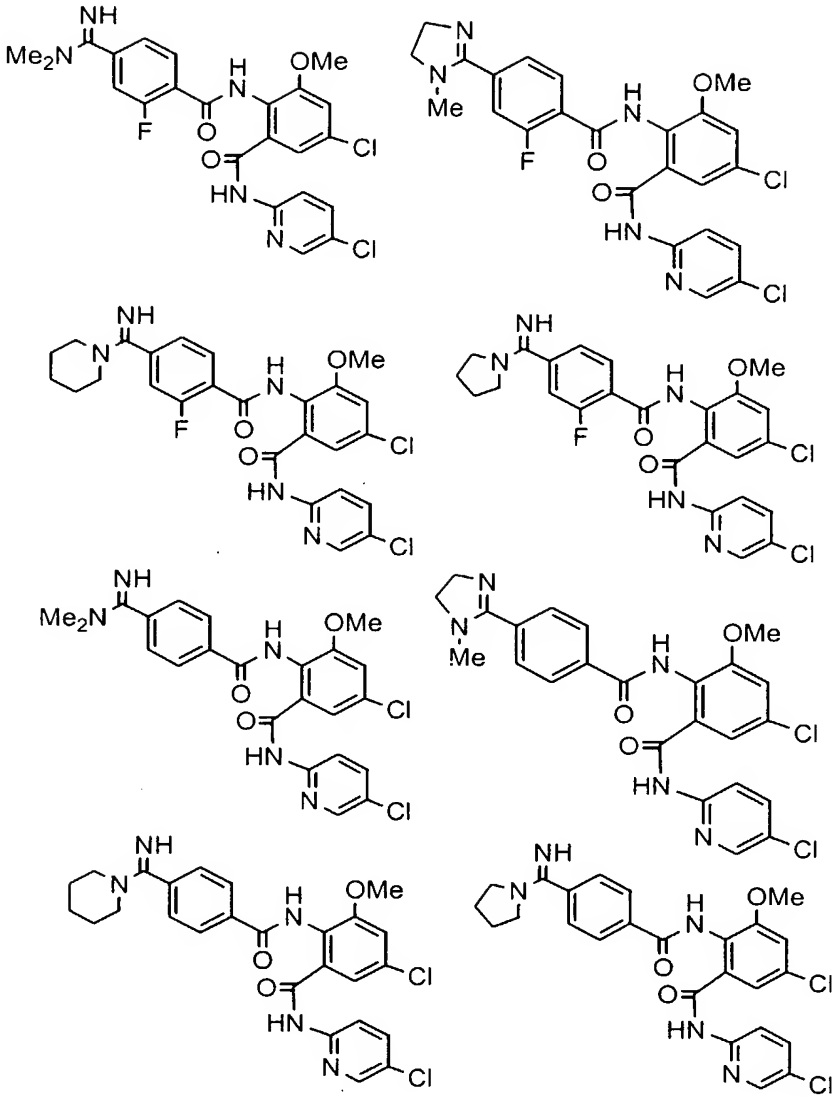
R^{1e} is a member selected from the group of -Cl, and -Br;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment according to the present invention provides an individual compound, which is a member selected from the following structures:



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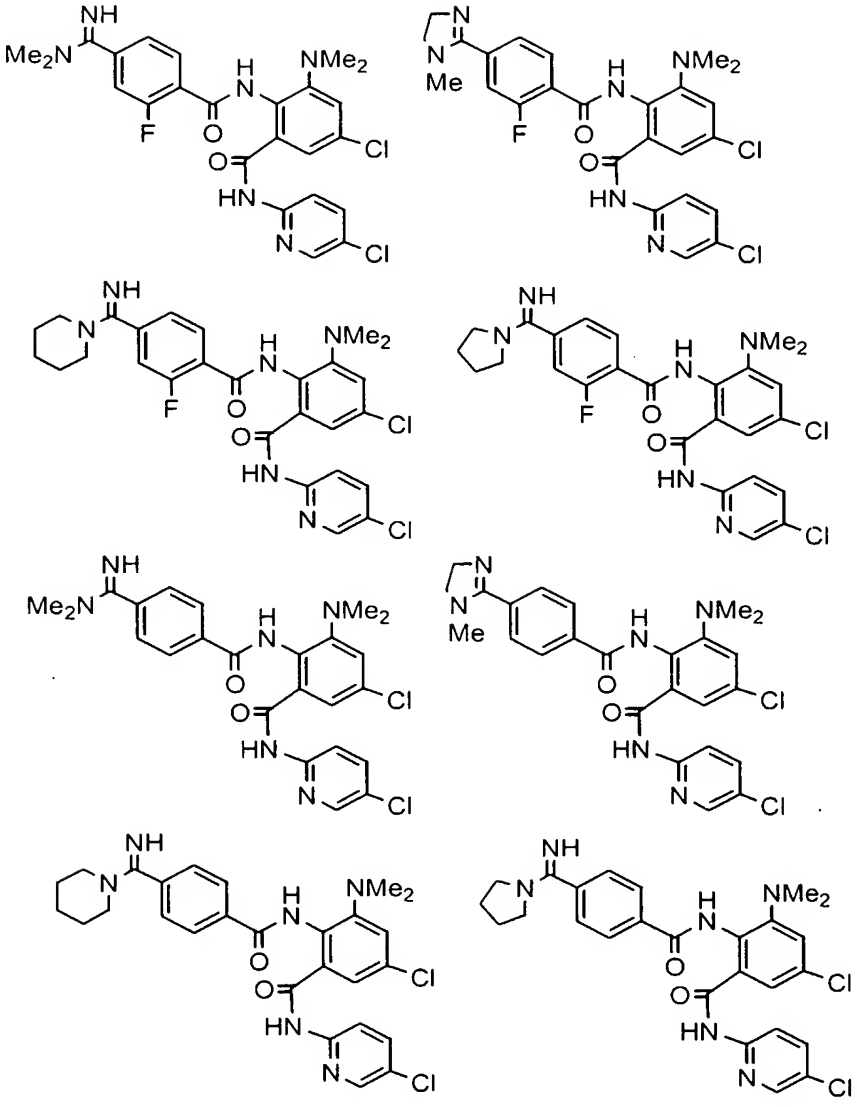
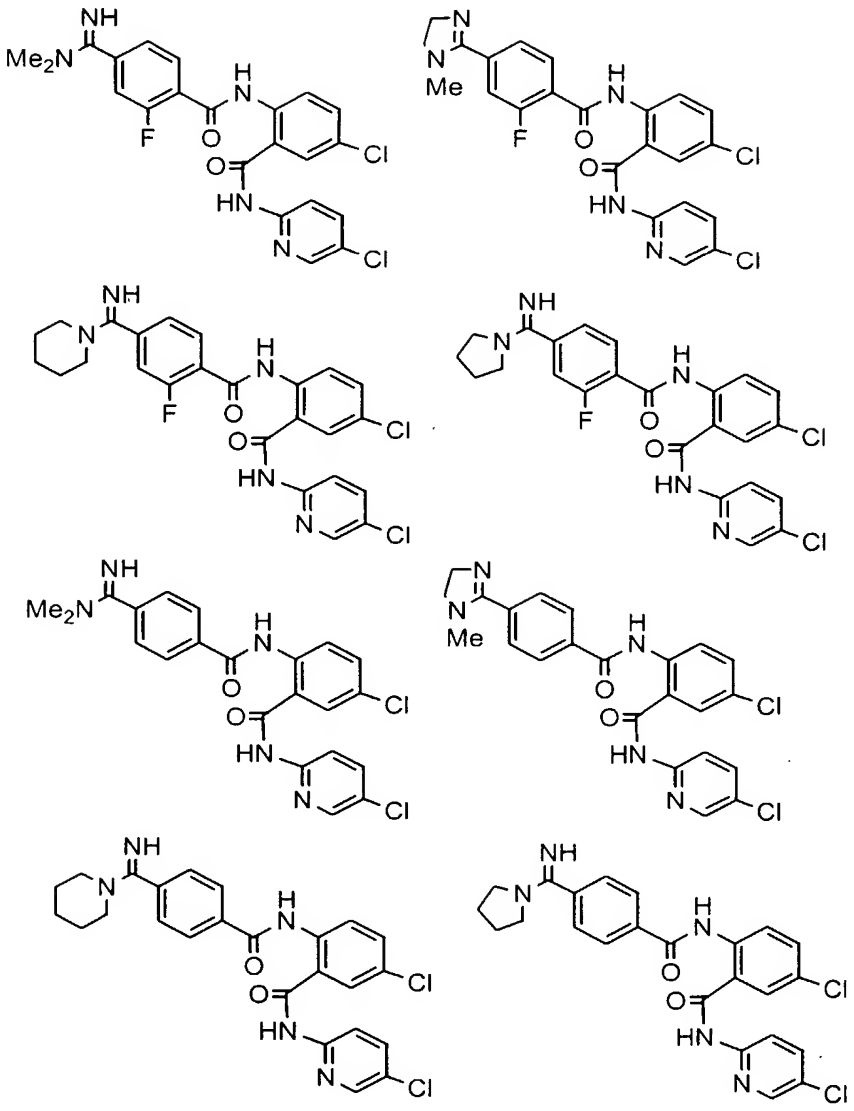
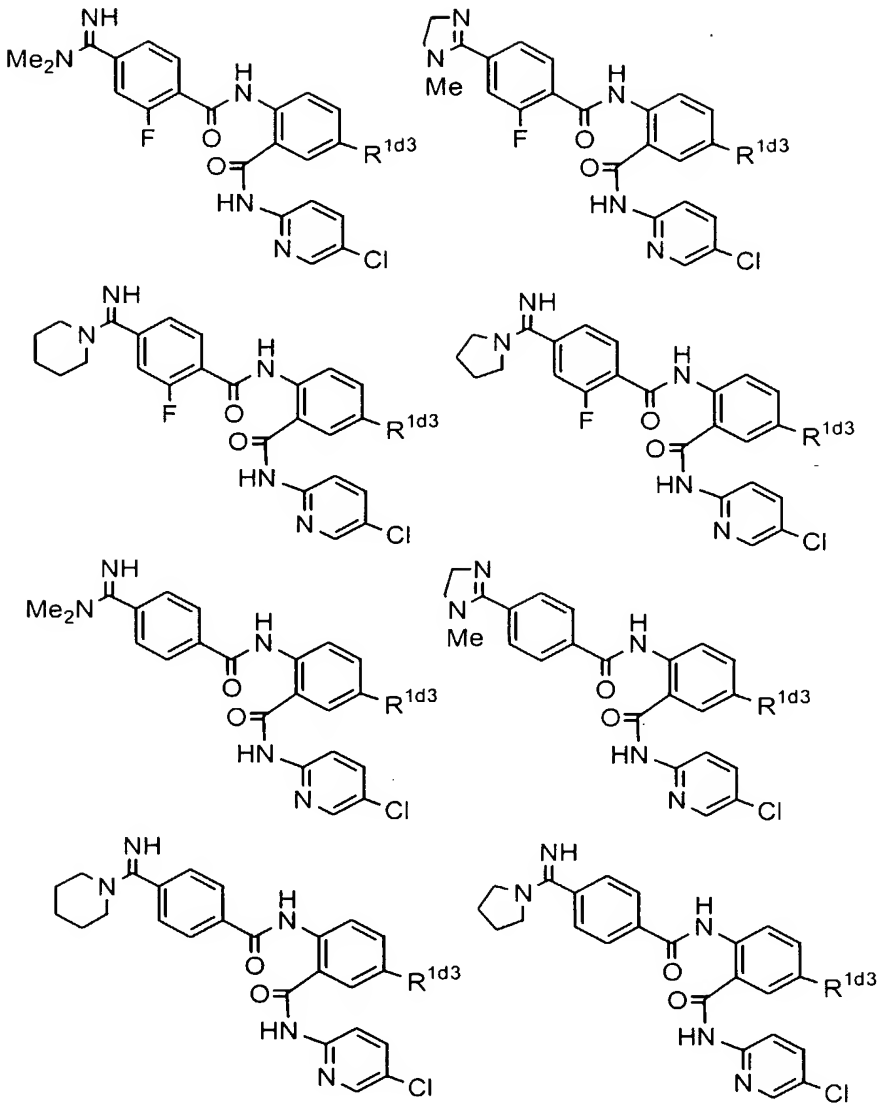






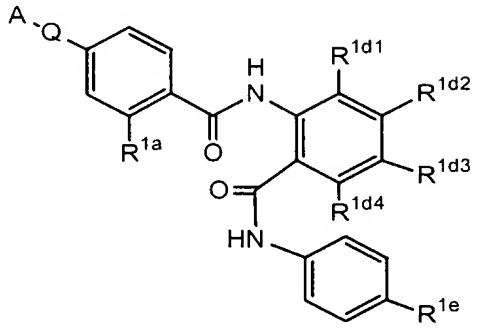
wherein

R^{1d3} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, $-OCF_3$, $-OCF_2H$, and $-OCF_2H$;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

A still further embodiment of the present invention provides a compound according to the formula IX, as follow:



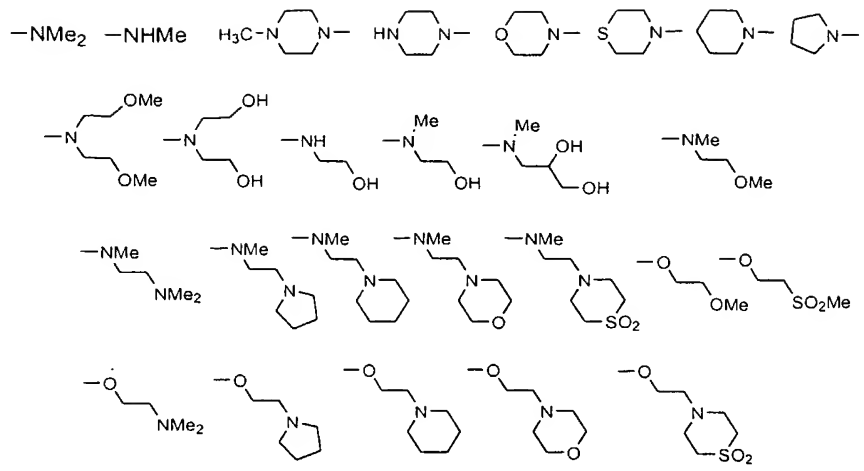
(IX')

wherein:

R^{1a} is a member selected from the group of H, -F, -Cl and Br;

R^{1d2} and R^{1d4} are each H or F;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H, -Cl, -F, -Br, -OH, -OMe, $-OCF_3$, $OCHF_2$, OCH_2F, $-NH_2$, $-NMe_2$, $-OCH_2COOEt$, $-OCH_2COOH$, $-N(Me)CH_2COOH$, -N(Me)COOEt,

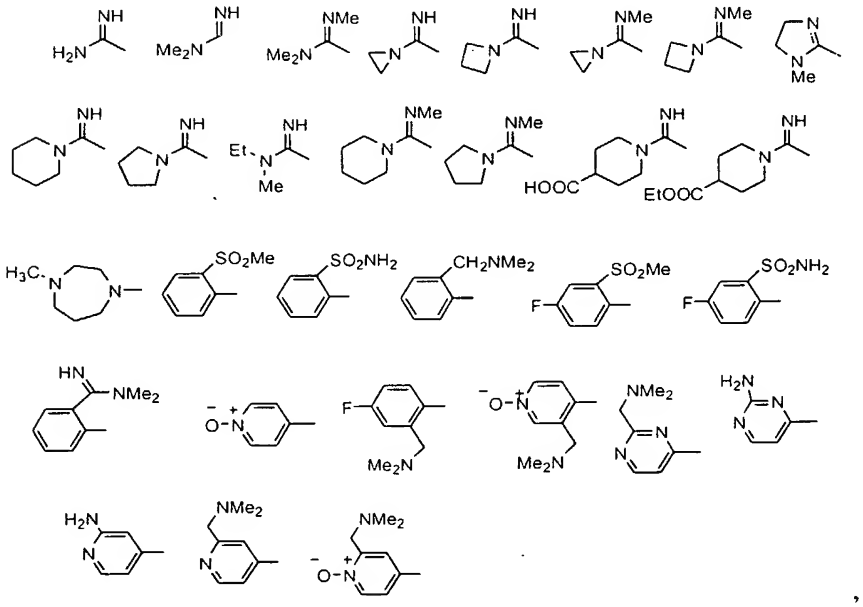


-N(Me)COOEt, -N(Me)CH2OOH,

;

R^{1e} is a member selected from the group of -F, -Cl, -Br, -OH, -Me and -OMe;

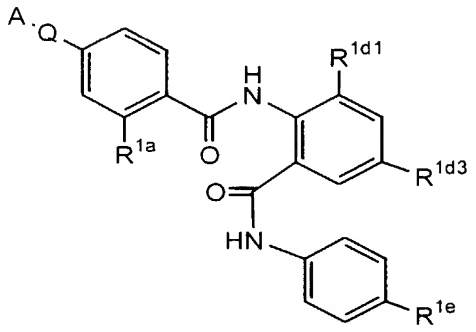
A-Q is a member selected from the group consisting of:



,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

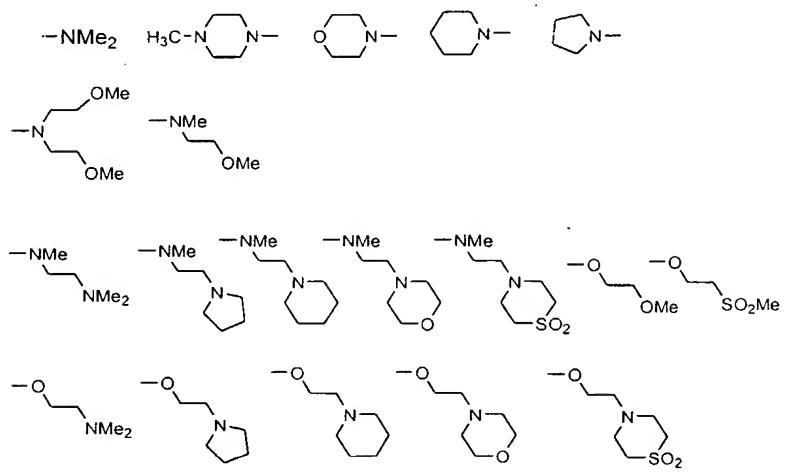
A particularly preferred embodiment of the present invention provides such compounds having the following formula:



wherein:

R^{1a} is a member selected from the group of H, or -F

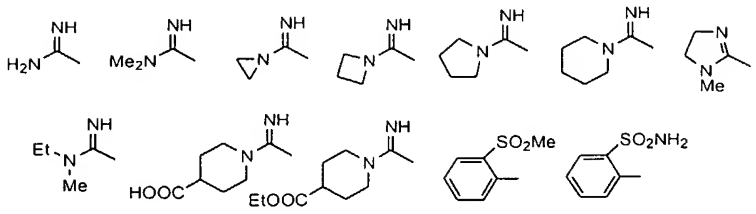
R^{1d1} is each independently a member selected from the group of H, -Cl, -OMe, $-NMe_2$, $-OCH_2COOEt$, $-OCH_2COOH$, - $N(Me)CH_2COOH$, -N(Me)COOEt, and,



R^{1d3} are independently a member selected from the group of H, -Cl, -Br, -F, and -OMe,

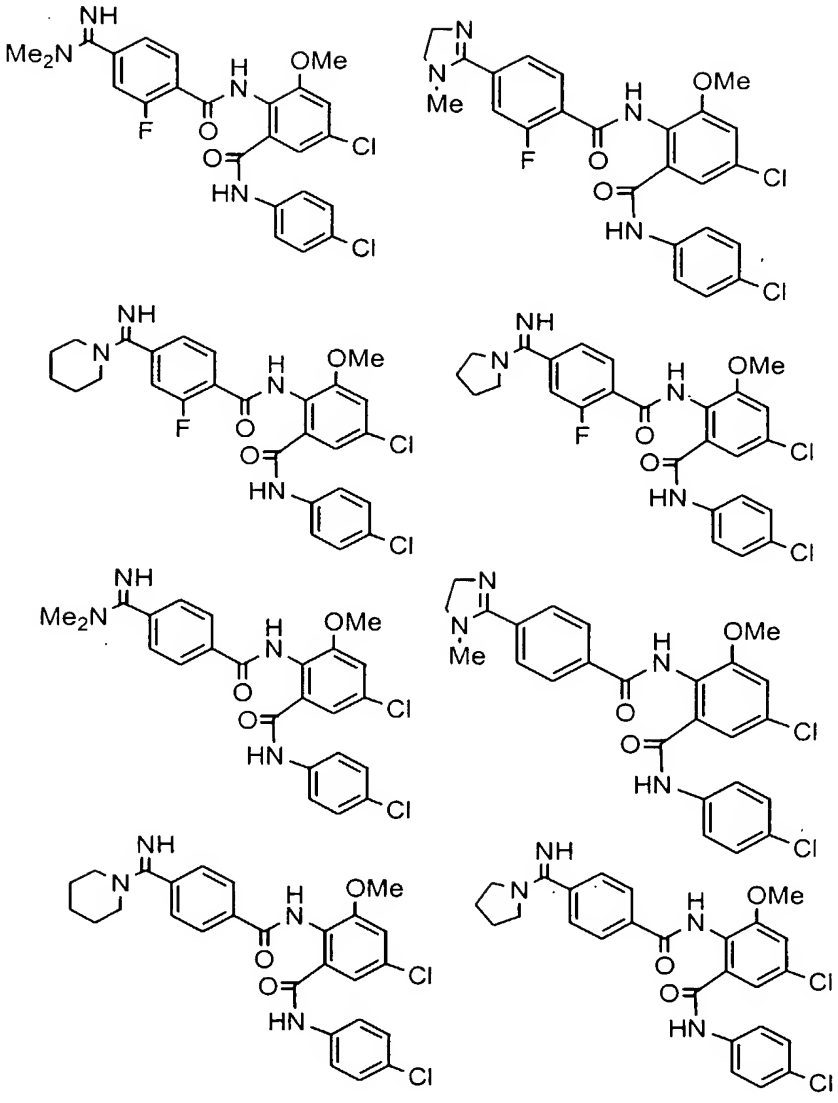
R^{1e} is a member selected from the group of -Cl, and -Br,

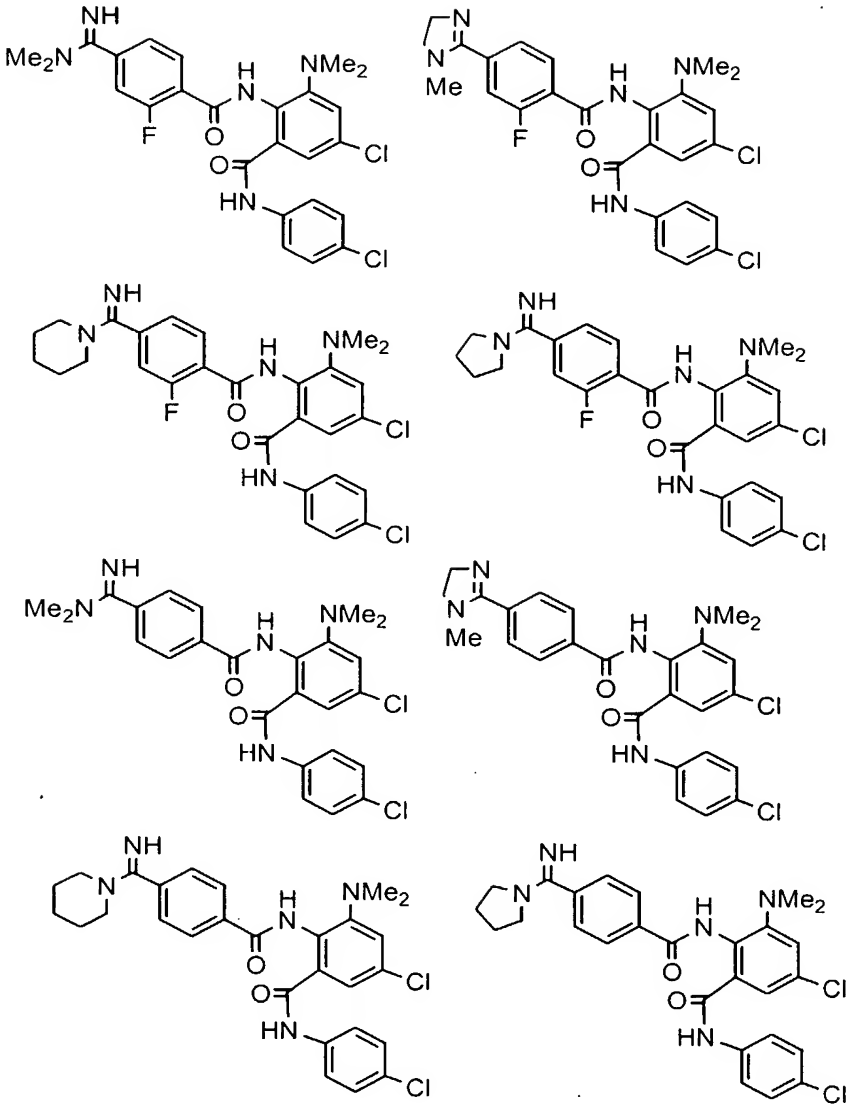
A-Q is a member selected from the group consisting of:

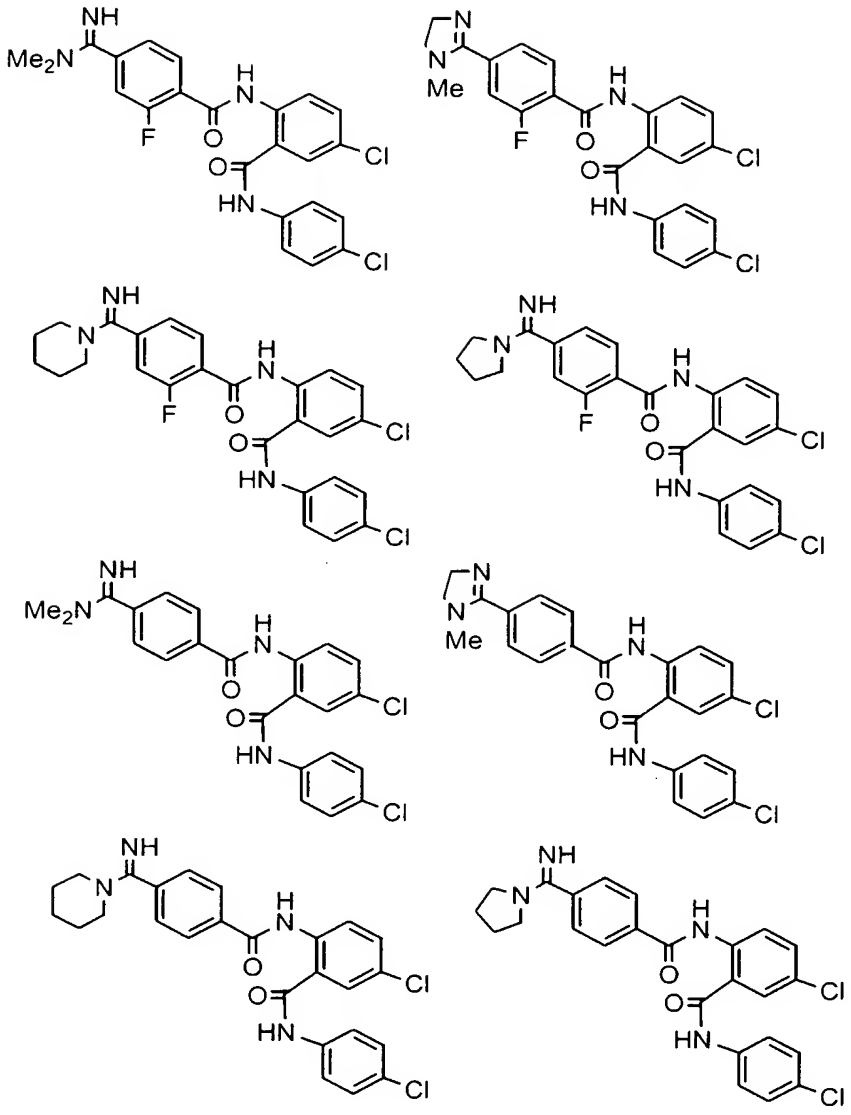


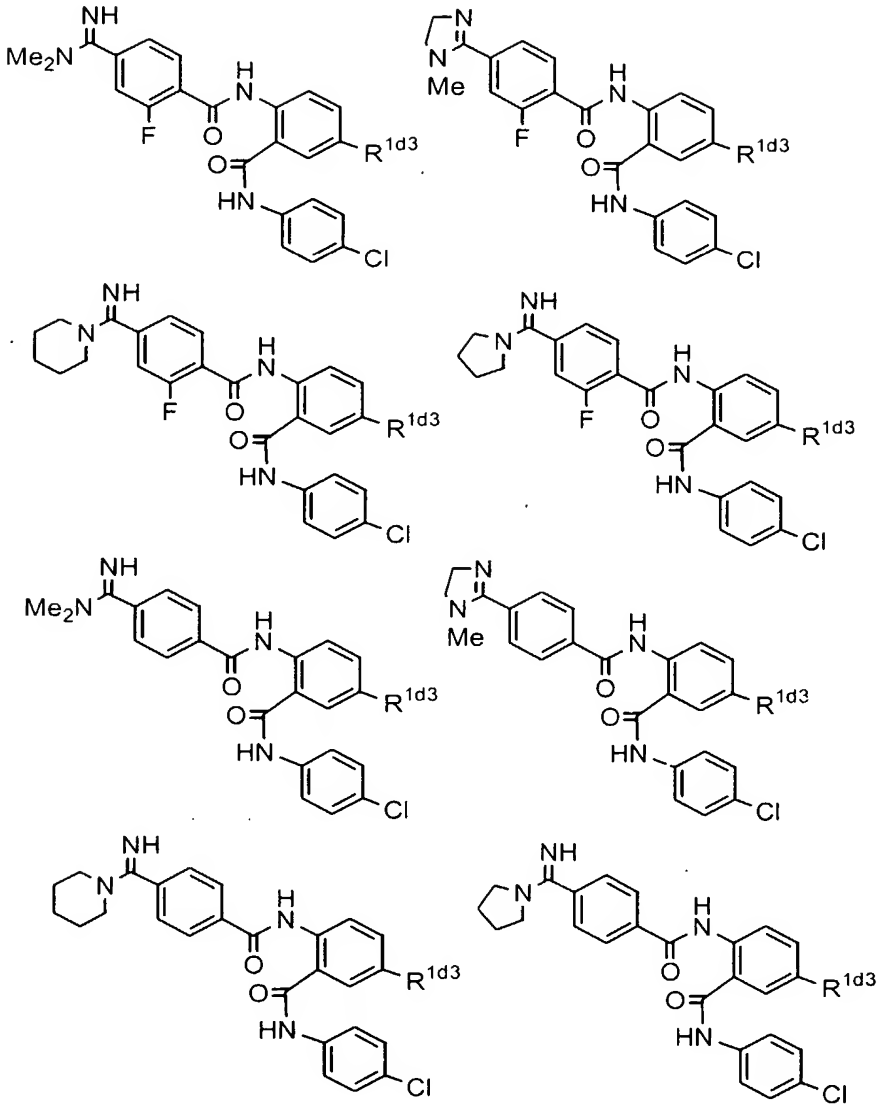
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

A still further embodiment of the present invention provides an individual compound which is a member selected from the following structures:









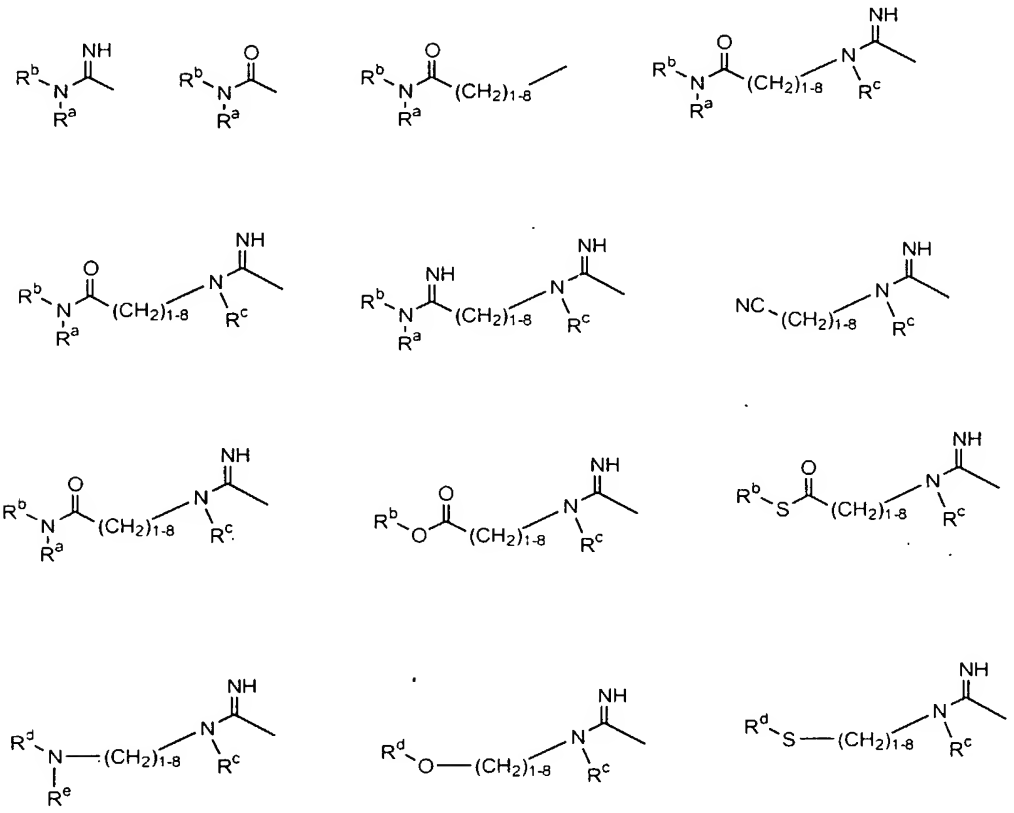
wherein

R^{1d3} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, $-OCF_3$, $-OCF_2H$, and $-OCF_2H$,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of the present invention provides compounds according to the invention as illustrated herein, wherein the A-Q- substituent is an amidinosubstituent, the amine portion of which is a cyclized amine heterocyclic ring, preferably a saturated cyclized amine heterocyclic ring, and the cyclized amine ring is substituted by 1-3 members. Examples of such A-Q substituents include but are not limited to:



wherein each of R^a, R^b, R^c, R^d and R^e is independently a member selected from the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_1-C_8 acyl and C_1-C_8 acyl C_1-C_8 alkyl ester, and the Ra and Rb groups together with the nitrogen atom to which they are both attached may be cyclized to form a C_3-C_8 heterocylic ring having from 1 to 4 additional hetero ring atoms selected from O, N and S,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment is an embodiment wherein the amidino groups illustrated above as substituents for the cyclized amine heterocyclic ring are instead form an acyclic amidino A-Q group and and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Such compounds are formed by reacting the appropriate acyclic amine or cycliczed amine with an amidino group or with a thioimino group wherein the remainder of the structures D-E-G-J-X are defined as in formula I or as in a preferred D-E-G-J-X structure illustrated in a preferred embodiment herein. Other ways to produce such compound structures will be apparent to an ordinary praticitioner in this field upon consideration of the description herein and the illustrated preferred embodiments.

This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives of the preferred compounds. In addition, the preferred compounds can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates, solvates, and prodrug derivatives of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative.

Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal

efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection,

other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Compounds according to the invention can be synthesized utilizing procedures well known in the art. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as

tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinalpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as

an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder,

preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of

coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary

embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

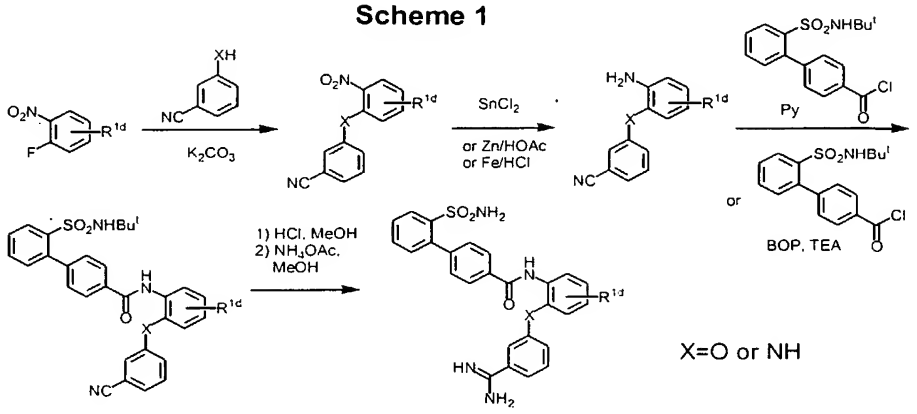
Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

EXAMPLES

Examples of Chemical Production Process General Reaction Schemes

Scheme 1



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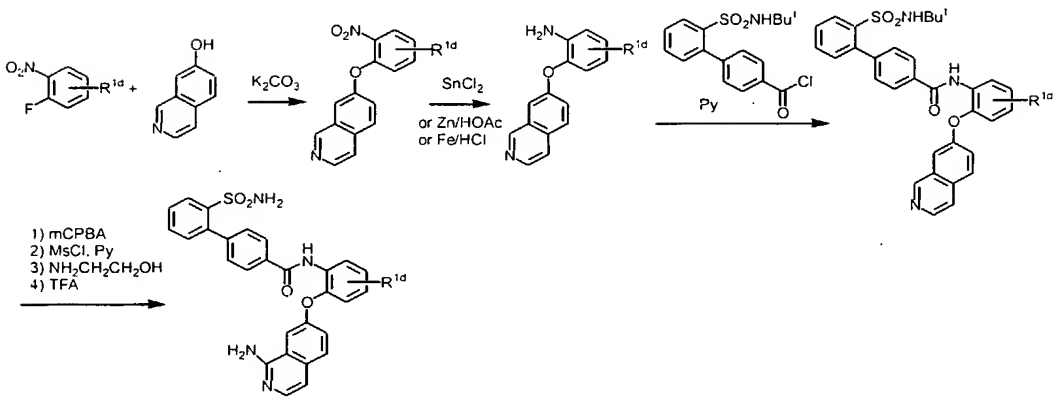
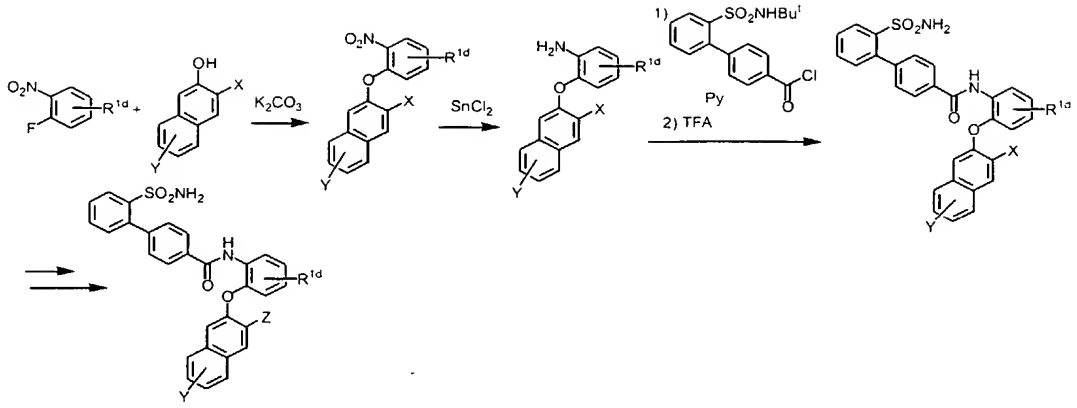
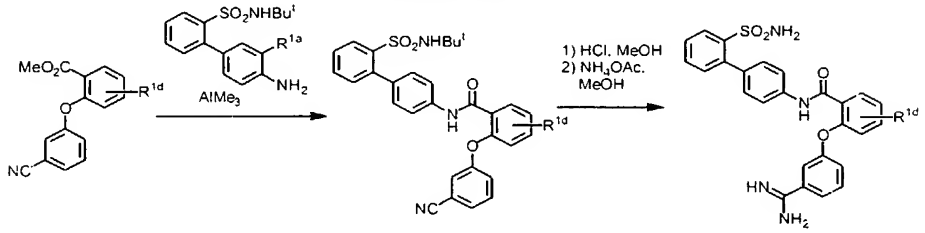
Scheme 2



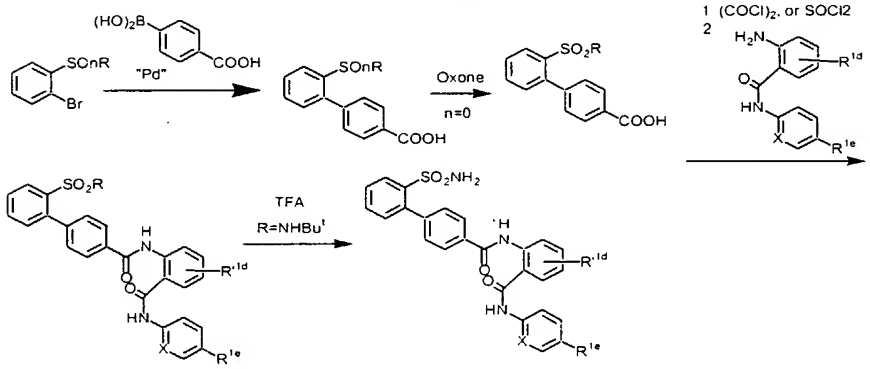
Scheme 3



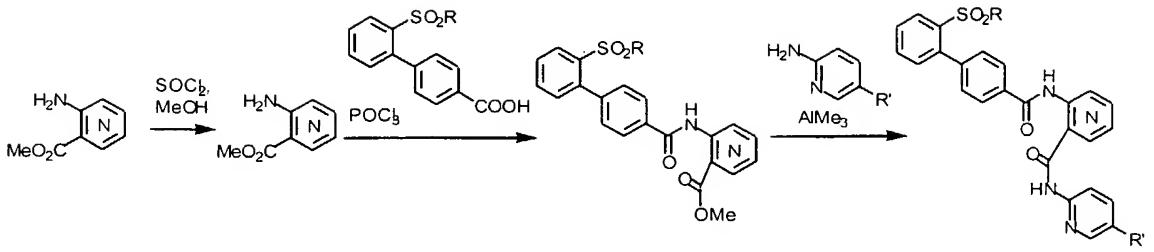
Scheme 4



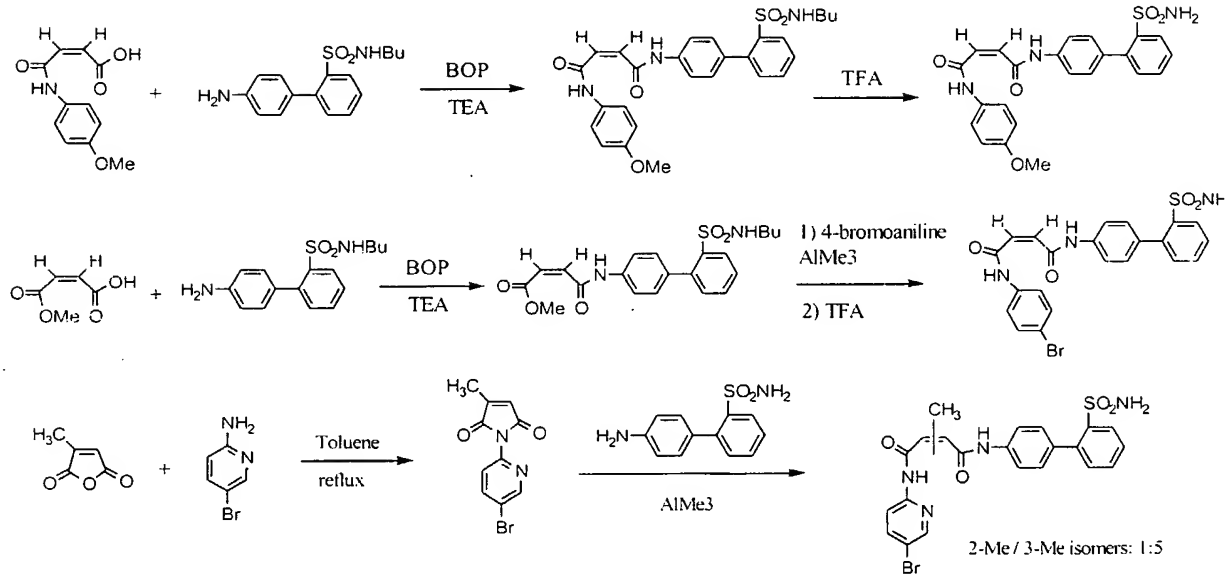
Scheme 5



Scheme 6



Scheme 7



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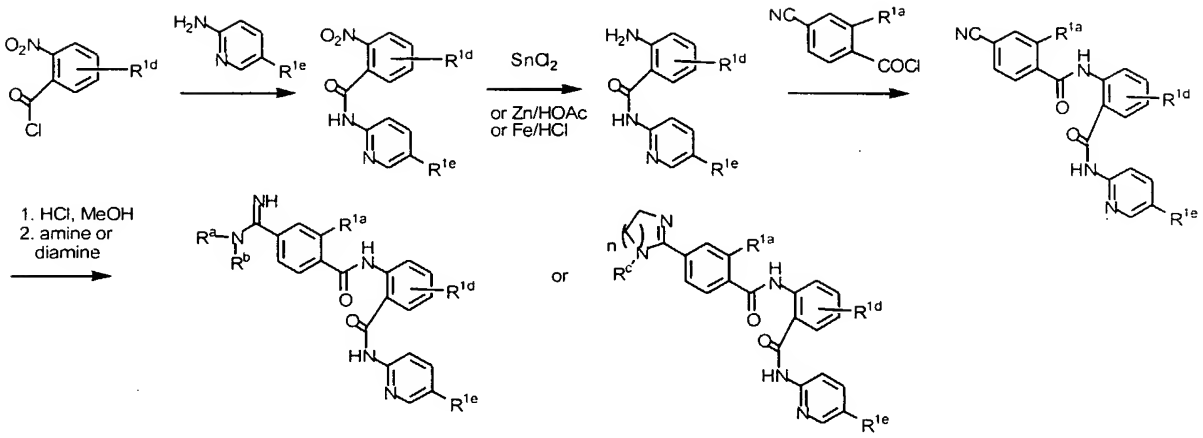
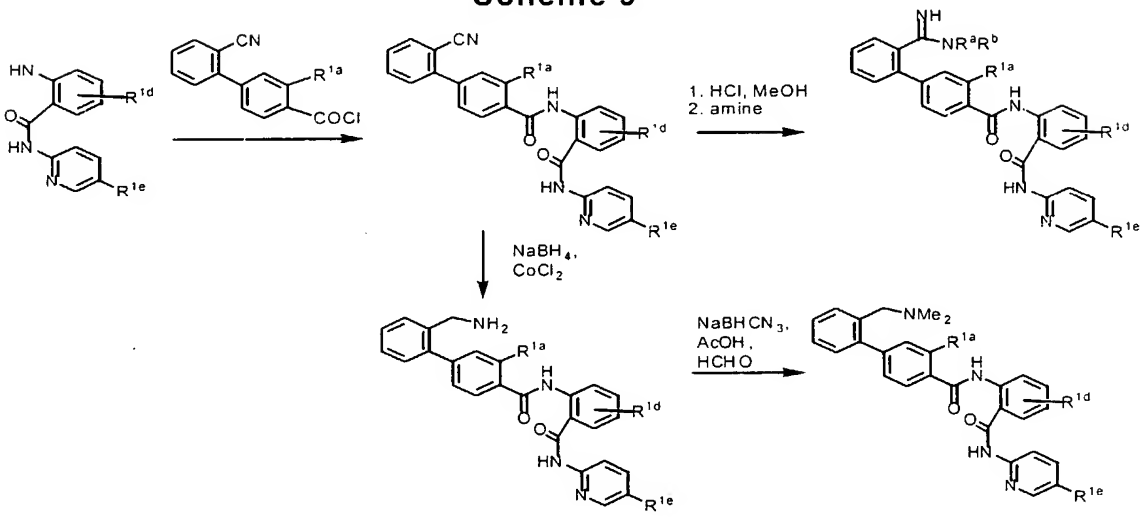
Scheme 8



Scheme 9



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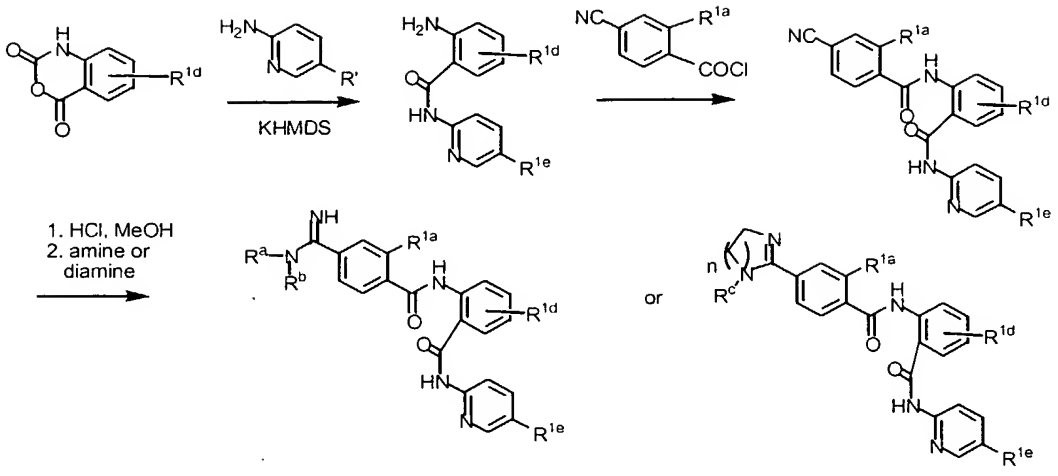
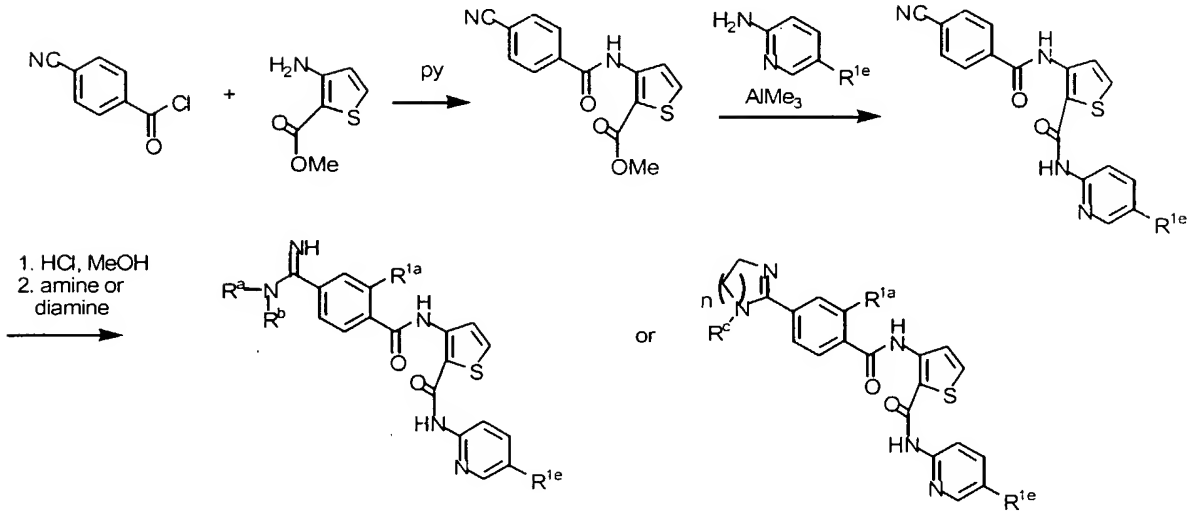
Scheme 10



Scheme 11



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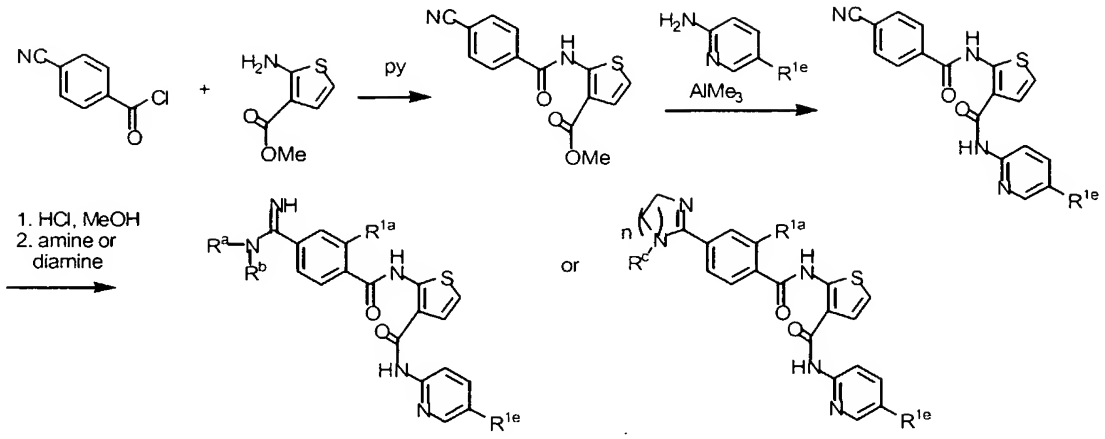
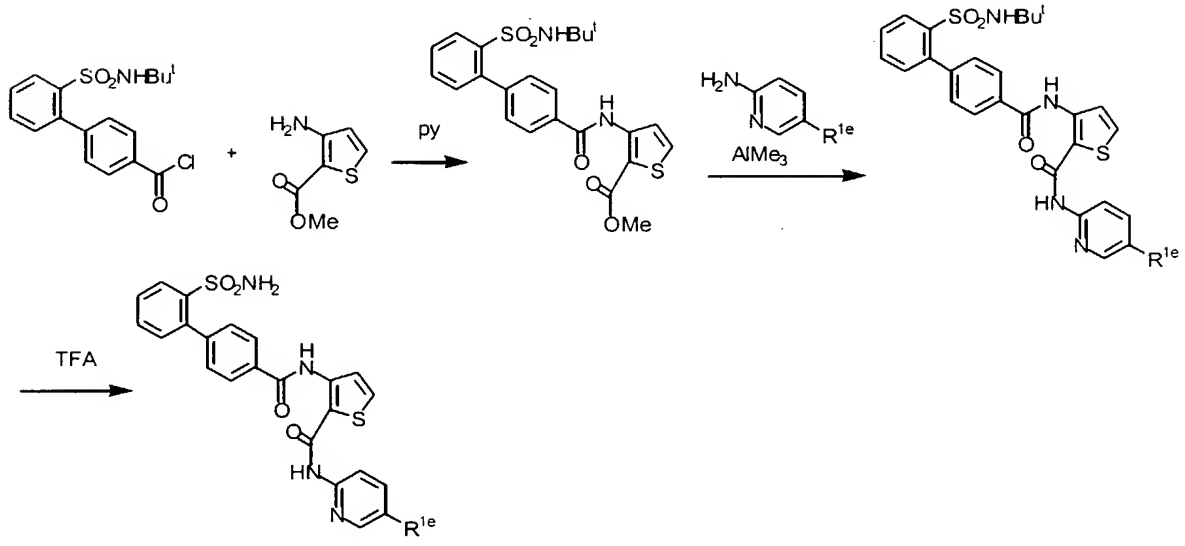
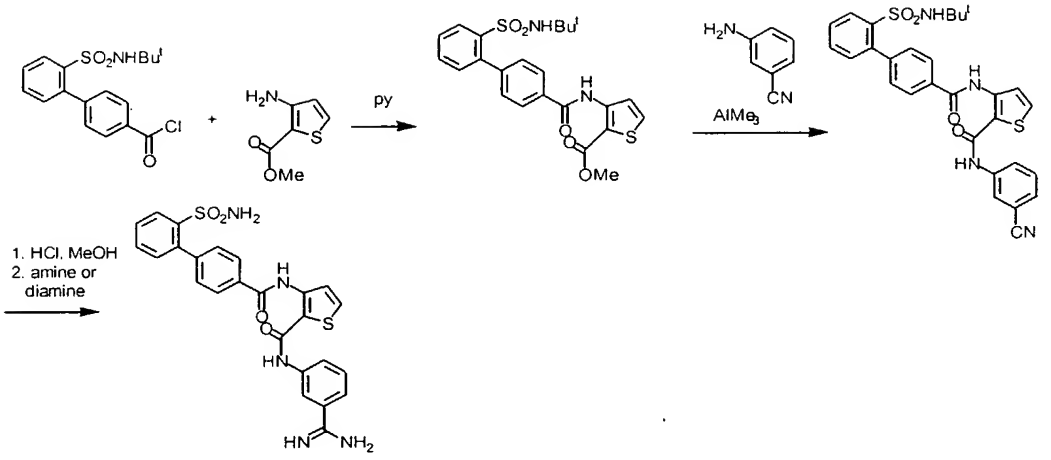
Scheme 12



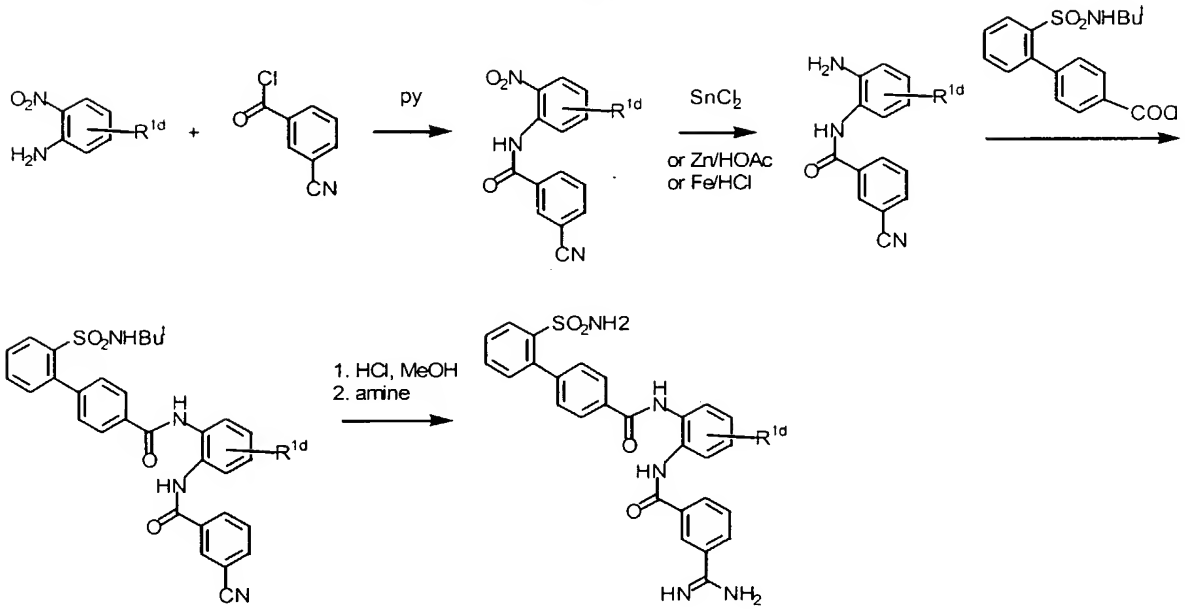
Scheme 13



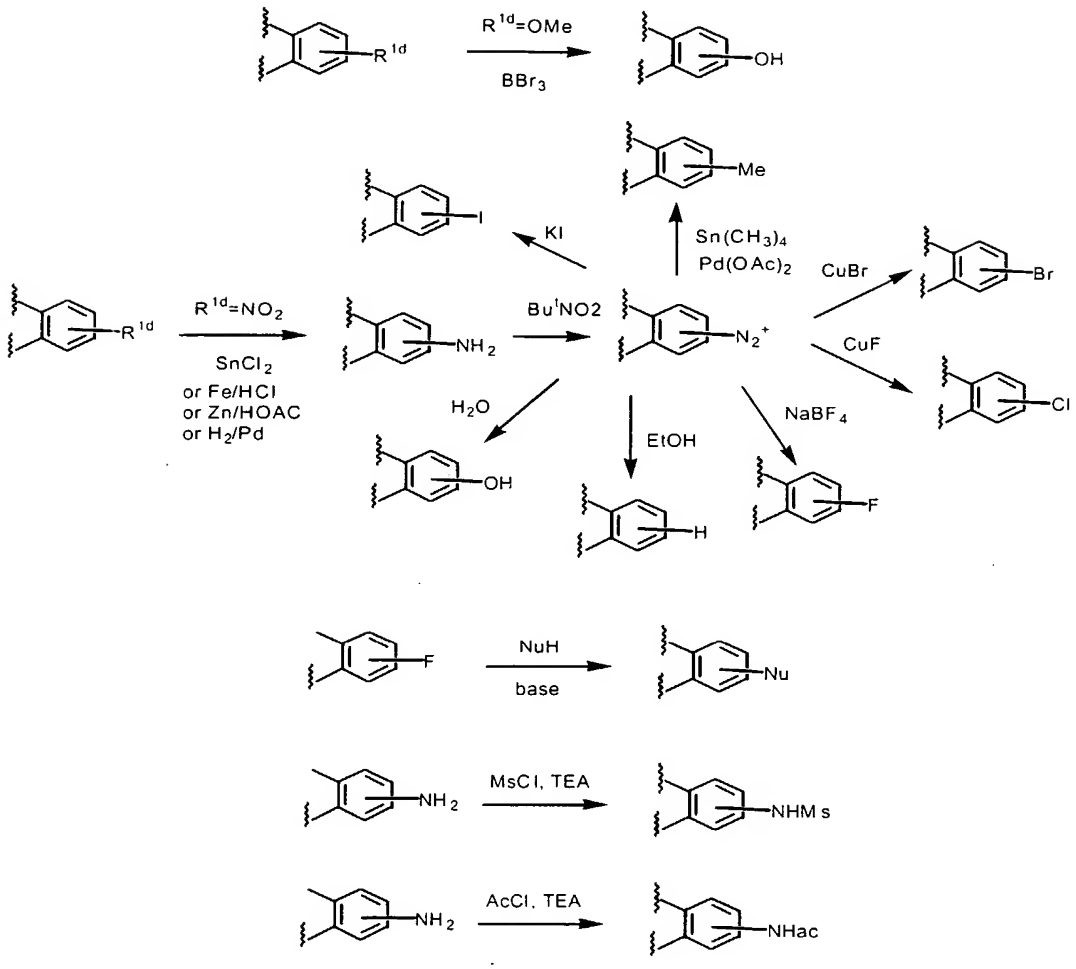
Scheme 14



Scheme 15

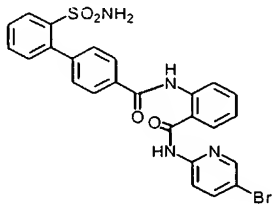


Scheme 16: Transformations of R^{1d}



Example 1

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



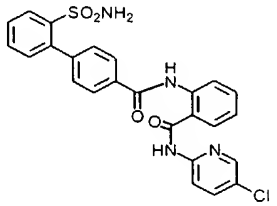
Step 1: A solution of 2-ntrobenzoyl chloride (3.70 g, 20 mmol, 1.0 equiv), 2-amino-5-bromopyridine (3.50 g, 1.0 equiv), pyridine (10 mL) in 25 mL of methylene chloride was stirred overnight. The volatile was evaporated, flash chromatography on silica gel gave N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (5.02 g, 77%). MS found for $C_{12}H_9BrN_3O_3$ $(M+H)^+$: 322.

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (1.0 g, 3.1 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_2 2H_2O$ (2.80 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (0.89 g, 98%). MS found for $C_{12}H_{11}BrN_3O$ $(M+H)^+$: 292.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (470 mg, 85%). MS found for $C_{25}H_{20}BrN_4O_4S$ $(M+H)^+$: 551.

Example 2

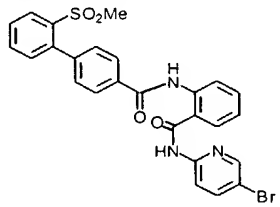
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



A mixture of N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (247 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (370 mg, 73%). MS found for $C_{25}H_{20}ClN_4O_4S$ $(M+H)^+$: 507.

Example 3

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



Step 1: To a mixture of 2-bromothioanisole (4.8g, 23.6mmol), 4-carboxybenzeneboronic acid (3.92g, 23.6mmol) and 2M K_2CO_3 (35.5mmol, 71mmol) in dioxane (20ml) was added dichlorobis(triphenylphosphine)palladium (II) (415mg, 0.6mmol) under Ar. It was refluxed for 2hrs. After the removal of the solvent, the residue was neutralized by 1N HCl and extracted with dichloromethane. The organic

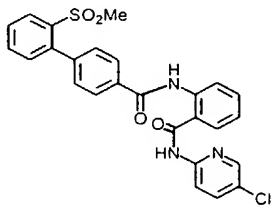
layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 4-[(2-methylthio)phenyl]benzoic acid (5.9g, 100%). ES-MS $(M+H)^+$=245.

Step 2: To a solution of 4-[(2-methylthio)phenyl]benzoic acid (3.43g, 14mmol) in H_2O (10ml) and acetone (20ml) was added oxone monopersulfate (34.6g, 56mmol). The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 2.16g (63%) 4-[(2-methylsulfonyl)phenyl]benzoic acid. ES-MS $(M+H)^+$=277.

Step 3: To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (552mg, 2mmol) in dichloromethane (5ml) was added oxalyl chloride (350ul, 4mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (700mg, 2.4mmol), pyridine (486ul, 6mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 414mg (38%) of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS M^+=550, $(M+2)^+$=552.

Example 4

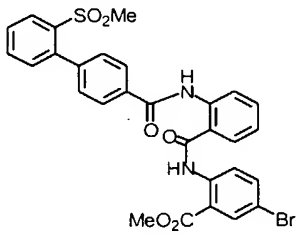
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol) in dichloromethane (5ml) was added oxalyl chloride (175 ul, 2 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (297mg, 1.2 mmol), pyridine (243ul, 3 mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 95 mg (20%) of N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS M+=505.5, (M+2)+=507.5.

Example 5

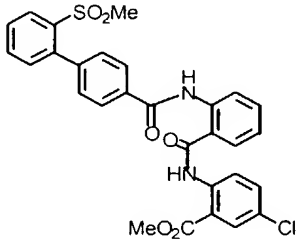
N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-bromo-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (348 mg,1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 480 mg (79%) of N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}BrN_2O_6S$ $(M+H)^+$: 607.

Example 6

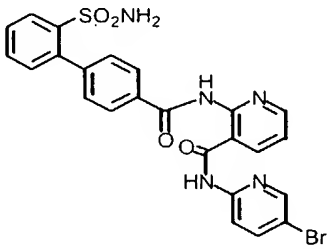
N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-chloro-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (304 mg,1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 479 mg (85%) of N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}ClN_2O_6S$ $(M+H)^+$: 563.

Example 7

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



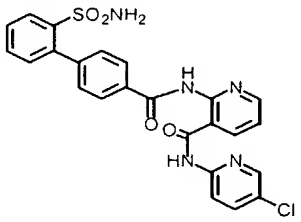
Step 1: A solution of 2-aminopyridine-3-carboxylic acid (138 mg, 1 mmol) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid and $POCl_3$. The

resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (243 mg, 52%). MS found for $C_{24}H_{26}N_3O_5S$ $(M+H)^+$: 468.

Step 2: To A solution of 2-amino-5-bromopridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (17 mg, 48%). MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 8

N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.

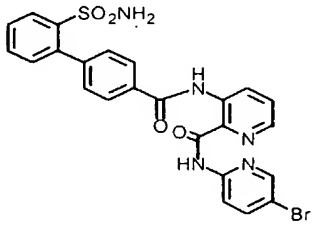


To A solution of 2-amino-5-chloropridine (32 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was

dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (21 mg, 66%). MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

Example 9

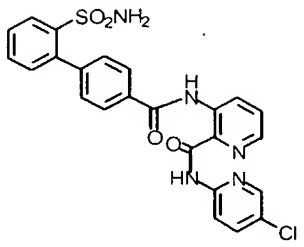
N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide.



To A solution of 2-amino-5-bromopridine (69.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide (29 mg, 53%). MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 10

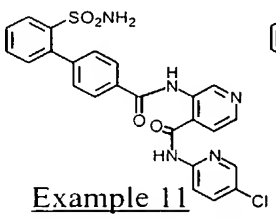
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



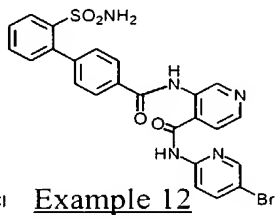
To A solution of 2-amino-5-chloropridine (51.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 0.1mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (33 mg, 64%). MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

Examples 11-14

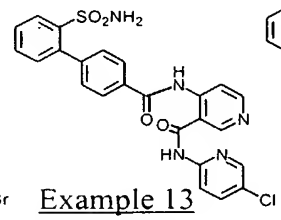
The following compounds were prepared using the procedure described previously:



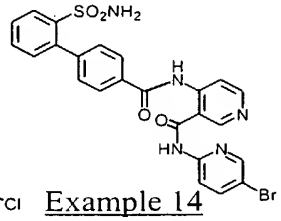
Example 11
MS (M+H): 508



Example 12
MS (M+H): 552



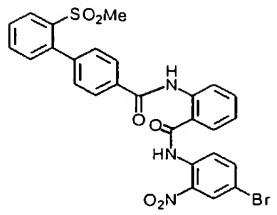
Example 13
MS (M+H): 508



Example 14
MS (M+H): 552

Example 15

N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.

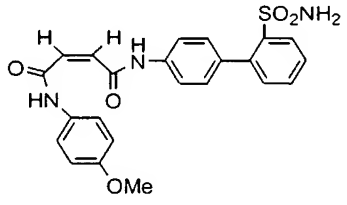


Step 1: A mixture of methyl 2-aminobenzoate (150 mg, 1 mmol, 1.0 equiv), 4-[(2-methylsulfonyl)phenyl]benzoic chloride (294 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (250 mg, 54%). MS found for $C_{25}H_{27}N_2O_5S$ $(M+H)^+$: 467.

Step 2: To a solution of 4-bromo-2-ntroaniline (43.4 mg, 0.2 mmol, 2.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.3 mL, 6 equiv) for 30 min was added methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (46.6 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide (5 mg, 9%). MS found for $C_{27}H_{21}BrN_3O_6S$ $(M+H)^+$: 594.

Example 16

N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide



A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)-maleamic amide.

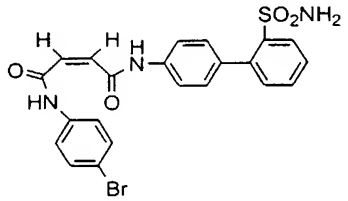
To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H2O, then with 5% NaHCO3, dried over Na2SO4, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH3CN in H2O (containing 0.1% TFA) to 100% CH3CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 (M + H).

B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)-maleamic amide (40 mg, 79 mol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M + H) and 474 (M + Na). ^{1}H NMR (CDCl3) δ 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J = 8 Hz), 7.72 (d, 2H, J = 8 Hz), 7.60 – 7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 17

N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.



A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester.

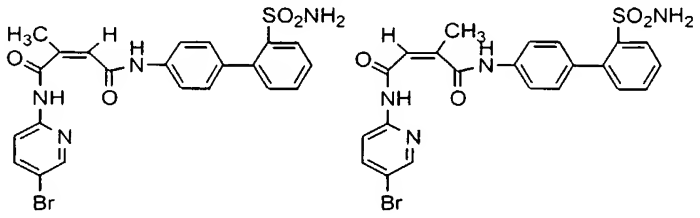
To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH2Cl2 (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH2Cl2 solution was then washed with sat. NaHCO3, 1N HCl and sat. NaCl. The solution was dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10-40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M + H - ^{t}Bu) and 439 (M + Na).

B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH2Cl2 (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M + H), 522 and 524 (M + Na). ^{1}H NMR (CD3OD) δ 8.09 (d, 1H, J = 8 Hz), 7.68 (d, 2H, J = 8 Hz), 7.64 – 7.28 (m, 9H), 6.45 (AB type, 2H).

Examples 18 and 19

Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl] phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.



A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

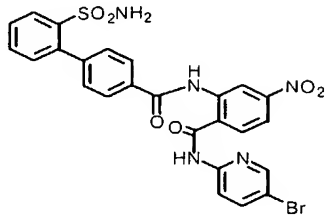
A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight. The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M + H).

B. Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl] phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.

To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH2Cl2 (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH2Cl2 (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2-3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1 : 5. MS 515 and 517 (M + H), 537 and 539 (M + Na).

Example 20

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide.

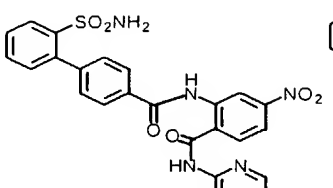


Step 1: A solution of 2-amino-4-nitrobenzoic acid (182 mg, 1 mmol, 1 equiv) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv) and $POCl_3$ (0.93 mL, 10 equiv). The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate *(430 mg, 84%)*. MS found for $C_{25}H_{26}N_3O_7S$ $(M+H)^+$: 512.

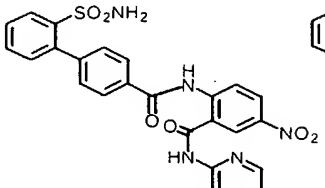
Step 2: To A solution of 2-amino-5-bromopridine (135 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 10 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (100 mg, 0.2 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide (42 mg, 36%). MS found for $C_{25}H_{19}BrN_5O_6S$ $(M+H)^+$: 596.

Examples 21-23

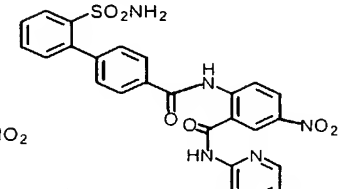
The following compounds were prepared according to the procedure described previously:



Example 21
MS (M+H): 552



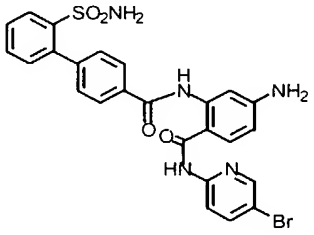
Example 22
MS (M+H):596



Example 23
MS (M+H):552

Example 24

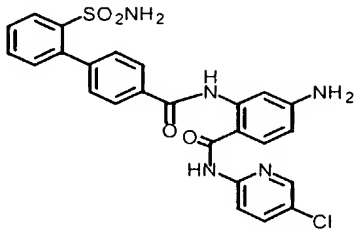
N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.



A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl] phenylcarbonyl) amino)-4-nitrophenylcarboxamide (65 mg, 0.1 mmol, 1 equiv) in 10 mL of EtOAc was treated with $SnCl_2 2H_2O$ (90 m g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide, which was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide (47 mg, 84%). MS found for $C_{25}H_{21}BrN_5O_4S$ $(M+H)^+$: 566.

Example 25

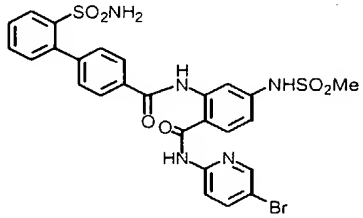
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.



This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}ClN_5O_4S$ $(M+H)^+$: 522.

Example 26

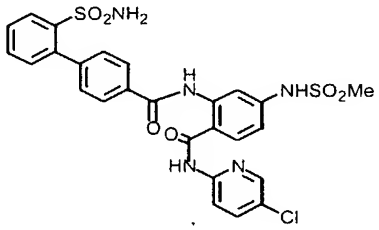
N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.



A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide (62 mg, 0.1mmol, 1 equiv) in 3 mL of CH_2Cl_2 was treated with MsCl (23 mg, 2 equiv) and TEA (0.5 mL) at rt for 4 h. The mixture was washed with water and dried over $MgSO_4$, filtered and evaporated. The residue was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide (33 mg, 52%). MS found for $C_{26}H_{23}BrN_5O_6S2$ $(M+H)^+$: 644.

Example 27

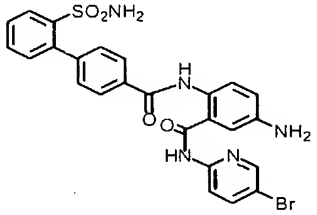
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.



This compound was prepared according to the procedure described in example 53. MS found for $C_{26}H_{23}ClN_5O_6S_2$ $(M+H)^+$: 600.

Example 28

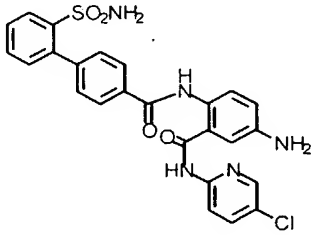
N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.



This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}BrN_5O_4S$ $(M+H)^+$: 566.

Example 29

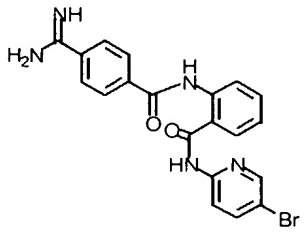
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.



This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}ClN_5O_4S$ $(M+H)^+$: 522.

Example 30

N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide.

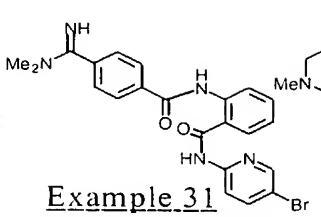


Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-cyano benzoyl chloride (165 mg, 1 equiv), pyridine *(3 mL)* in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (349 mg, 70%). MS found for $C_{20}H_{14}BrN_4O_2$ $(M+H)^+$: 421.

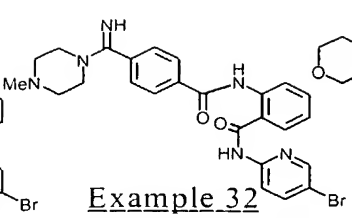
Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide (31 mg, 70%). MS found for $C_{20}H_{17}BrN_5O_2$ $(M+H)^+$: 438.

Examples 31-60

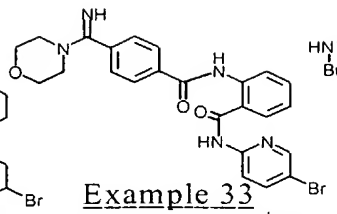
The following compounds were prepared according to the procedure described previously



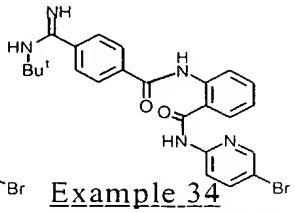
Example 31
MS (M+H):466



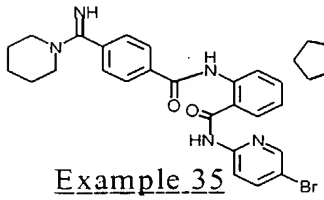
Example 32
MS (M+H): 521



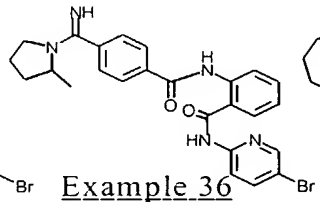
Example 33
MS (M+H):508



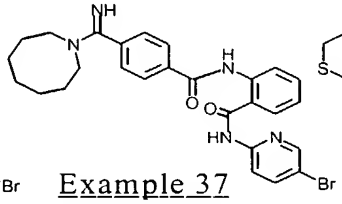
Example 34
MS (M+H): 494



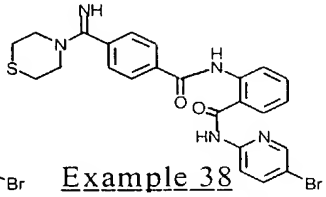
Example 35
MS (M+H):506



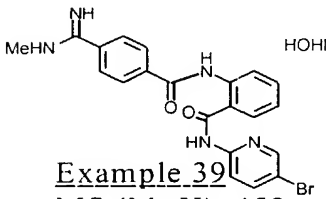
Example 36
MS (M+H): 506



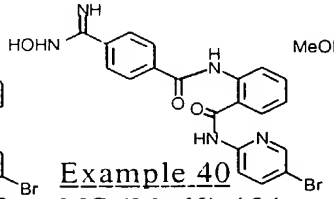
Example 37
MS (M+H):520



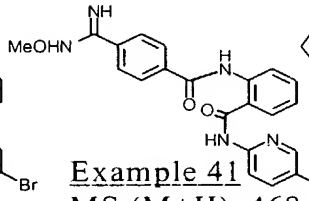
Example 38
MS (M+H): 524



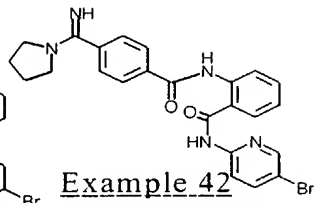
Example 39
MS (M+H): 452



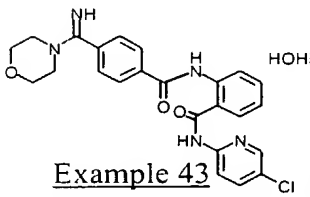
Example 40
MS (M+H):454



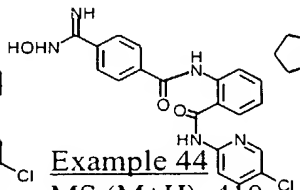
Example 41
MS (M+H): 468



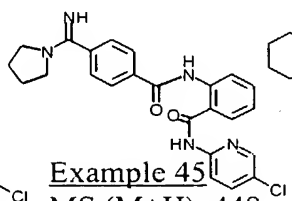
Example 42
MS (M+H):492



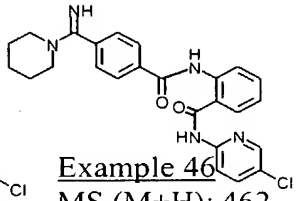
Example 43
MS (M+H): 464



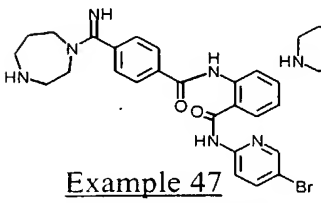
Example 44
MS (M+H): 410



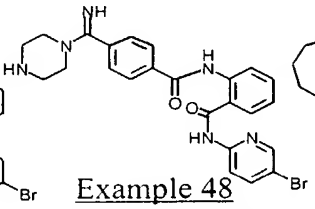
Example 45
MS (M+H): 448



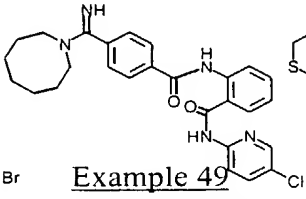
Example 46
MS (M+H): 462



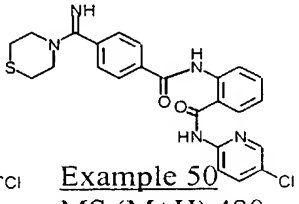
Example 47
MS (M+H): 521



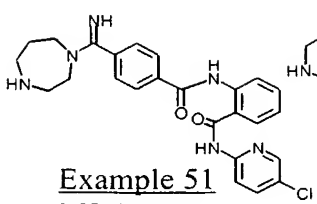
Example 48
MS (M+H):507



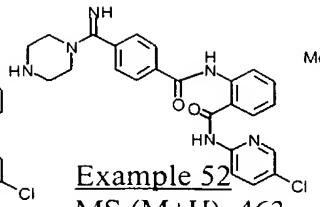
Example 49
MS (M+H):476



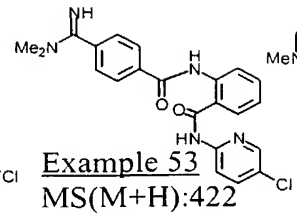
Example 50
MS (M+H):480



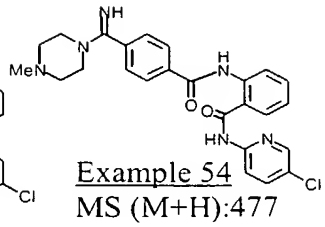
Example 51
MS (M+H): 477



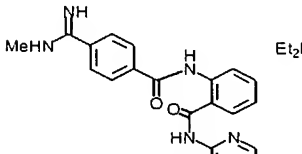
Example 52
MS (M+H): 463



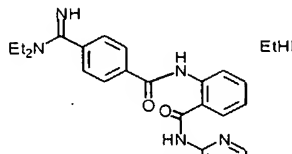
Example 53
MS(M+H):422



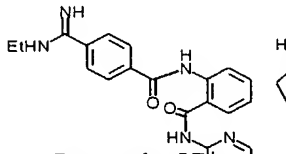
Example 54
MS (M+H):477



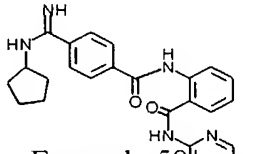
Example 55
MS (M+H): 408



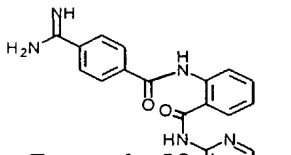
Example 56
MS (M+H): 22



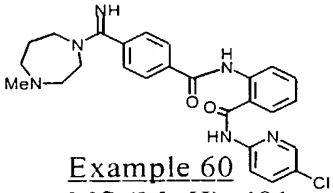
Example 57
MS (M+H): 450



Example 58
MS (M+H): 462



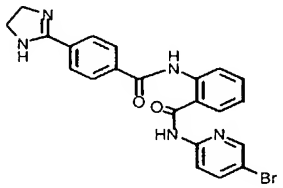
Example 59
MS (M+H): 394



Example 60
MS (M+H): 491

Example 61

N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide.

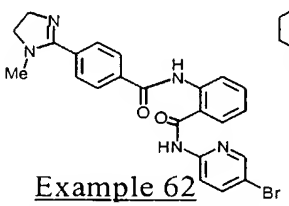


A stream of HCl(g) was bubbled through a 0^0C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ethylene diamine (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(2-

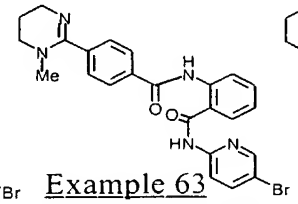
imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide (41 mg, 89%). MS found for $C_{22}H_{19}BrN_5O_2$ $(M+H)^+$: 464.

Examples 62-70

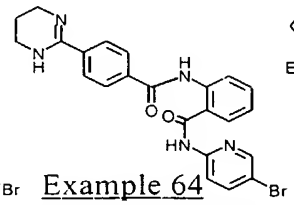
The following compounds were prepared according to the procedure previously described



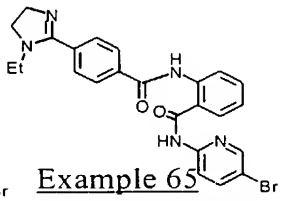
Example 62
MS (M+H): 478



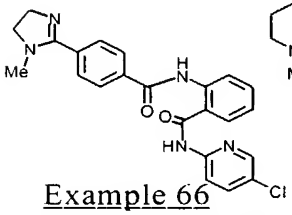
Example 63
MS (M+H): 492



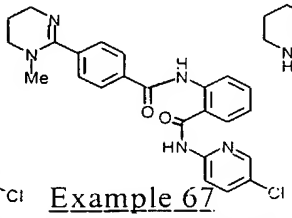
Example 64
MS (M+H): 478



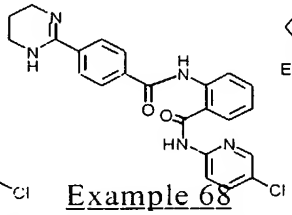
Example 65
MS (M+H): 492



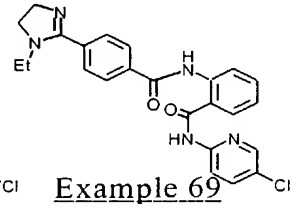
Example 66
MS (M+H): 434



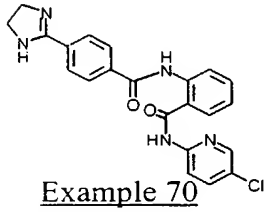
Example 67
MS (M+H): 448



Example 68
MS (M+H): 434



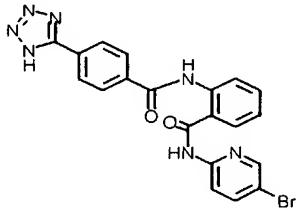
Example 69
MS (M+H): 448



Example 70
MS (M+H): 420

Example 71

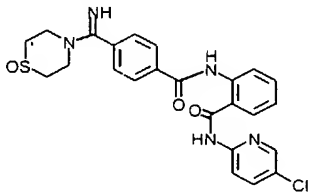
N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide.

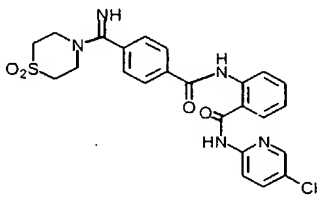


A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) and sodium azide (67 mg, 10 equiv) in 5 mL of DMF was heated at 100^{0}C for 24h. The reaction mixture was diluted with EtOAc, washed with water, dried, filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide (33 mg, 65%). MS found for $C_{20}H_{15}BrN_7O_2$ $(M+H)^+$: 464.

Example 72 and Example 73

N-(5-bromo-2-pyridinyl)-(2-(4[-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide and **N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide.**

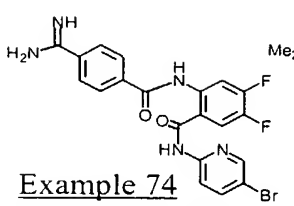




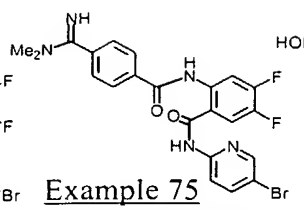
A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-(1,4-thiazaperhydroin-4-yl)iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (48 mg, 0.1 mmol) and and 3 mL of 30% hydrogen doxide was stirred at rt for 12h. The reaction was quenched with solid $Na_2S_2O_3$. Purification by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-(4[-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (15 mg, 31%), MS found for $C_{24}H_{23}ClN_5O_4S$ $(M+H)^+$: 512 and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (20 mg, 41%). MS found for $C_{24}H_{23}ClN_5O_3S$ $(M+H)^+$: 496.

Examples 74-79

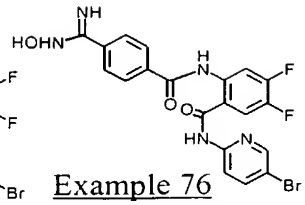
The following compounds were prepared according to the procedure previously described



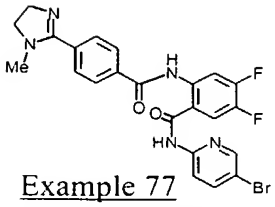
Example 74
MS (M+H): 474



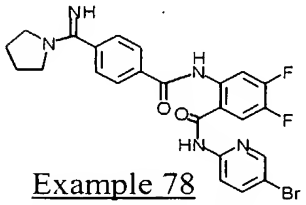
Example 75
MS (M+H): 502



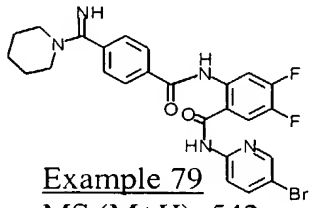
Example 76
MS (M+H): 490



Example 77
MS (M+H): 514



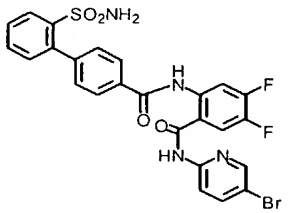
Example 78
MS (M+H): 528



Example 79
MS (M+H): 542

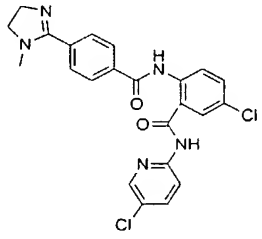
Example 80

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-4,5-difluorophenylcarboxamide.



This compound was prepared according to the procedure previously described. MS found for $C_{25}H_{18}BrF_2N_4O_4S$ $(M+H)^+$: 587.

Example 81



Step 1: To a solution of 2-amino-5-chloropyridine (328mg, 2.55mmol) in tetrahydrofuran (5ml) was 0.5M potassium bis(trimethylsilyl)amide in toluene (10ml, 5.05mmol) dropwise at –78 °C. After stirred for additional 0.5hr at –78 °C, the

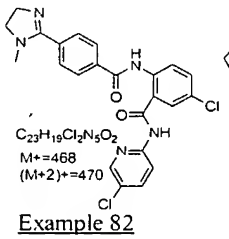
mixture was added 5-chloroisatoic anhydride (0.5g, 2.55mmol) at –78 °C. The mixture was warmed up to r.t gradually and stirred overnight. After quenched by saturated ammonium chloride solution, the mixture was extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g. 100%). MS found for C12H9Cl2N3O M^+=282, $(M+2)^+$=284.

Step 2: To a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 2.52mmol) in dichloromethane (10ml) was added 3-cyanobenzoly chloride (417mg, 2.52mmol) and pyridine (0.611ml, 7.55mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide as a solid (683mg, 66%). MS found for C20H12Cl2N4O2 M^+=411, $(M+2)^+$=413.

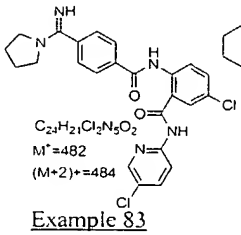
Step 3: To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (683mg, 1.66mmol) in anhydrous pyridine (10ml) and triethyl amine (1ml) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous acetone (5ml) and iodomethane (1ml, 16.6mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the residue was dissolved in anhydrous methanol (5ml) and added a solution of N-methylethylenediamine (0.732ml, 8.3mmol) and acetic acid (1.5ml) in anhydrous methanol (5ml).The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for C23H19Cl2N5O2 M^+=468 $(M+2)^+$=470.

Examples 82-106

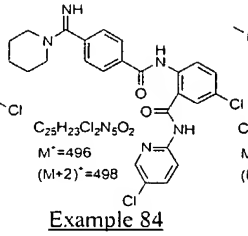
The following compounds were prepared according to the procedure previously described



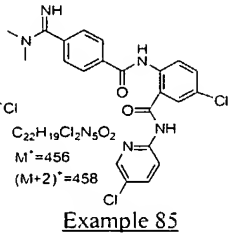
Example 82



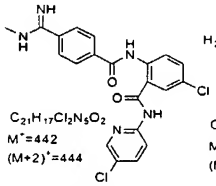
Example 83



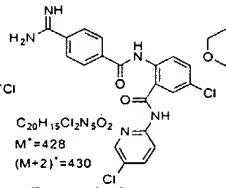
Example 84



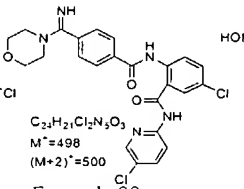
Example 85



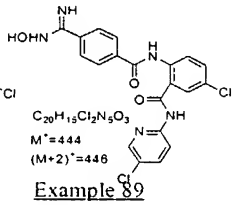
Example 86



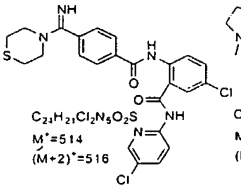
Example 87



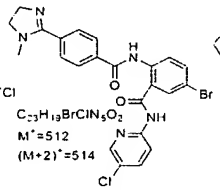
Example 88



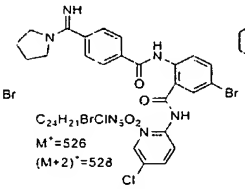
Example 89



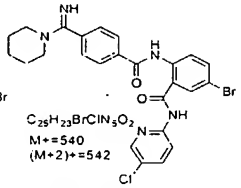
Example 90



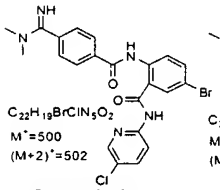
Example 91



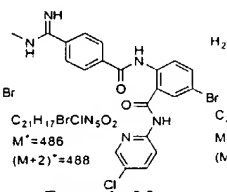
Example 92



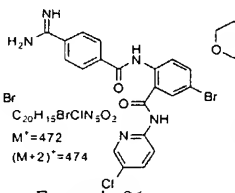
Example 93



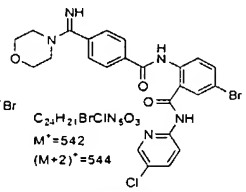
Example 94



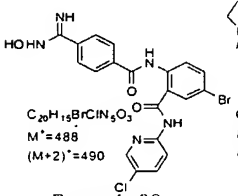
Example 95



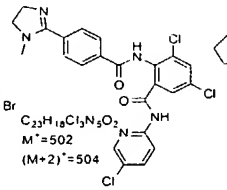
Example 96



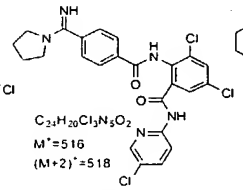
Example 97



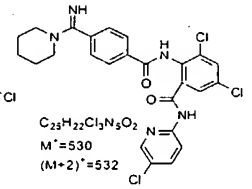
Example 98



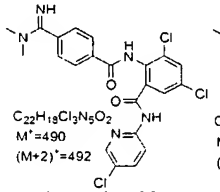
Example 99



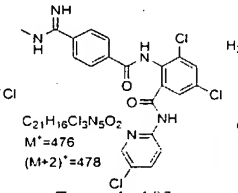
Example 100



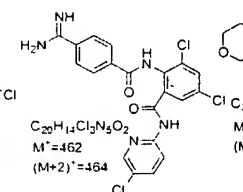
Example 101



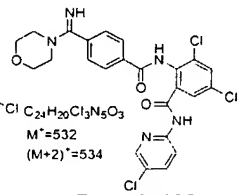
Example 102



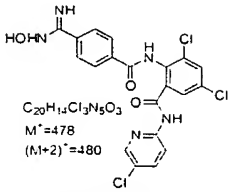
Example 103



Example 104

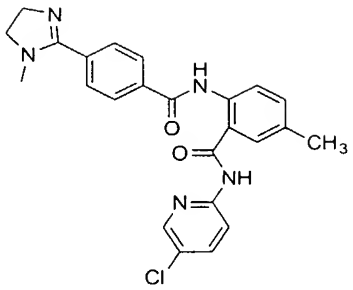


Example 105



Example 106

Example 107



Step 1: To a solution of 5-methyl-2-nitrobenzoic acid (1g, 5.52mmol) in dichloromethane (5ml) was added oxalyl chloride (0.964ml, 11.04mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-chloropyridine (852mg, 6.62mmol) and pyridine (1.34ml, 16.56mmol) were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide as a solid (1.48g, 92%). MS found for C13H10ClN3O3 M^+=291, $(M+2)^+$=293.

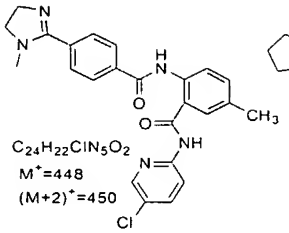
Step 2: To a solution of the compound of N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide (1.48g, 5.1mmol) in methanol (10ml) was added 5% Pt/C (1.48g, 0.19mmol). The mixture was applied hydrogen balloon at r.t.for 2 hrs. After the filtration by Celite, the filtrate was concentrated to give (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 100%). MS found for C13H12ClN3O M^+=262, $(M+2)^+$=264.

Step 3: To a solution of the compound of (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 5.2mmol) in dichloromethane (10ml) was added 3-cyanobenzoly chloride (860mg, 5.2mmol) and pyridine (1.26ml, 15.6mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide as a solid (830mg, 41%). MS found for C21H15ClN4O2 M^+=390, $(M+2)^+$=392.

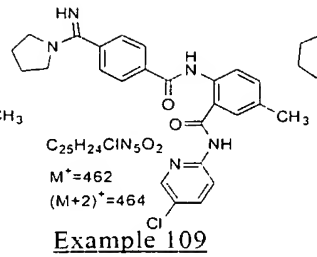
Step 4: To a lotion of the compound of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide (830mg, 2.1mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.926ml, 10.5mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for C24H22ClN5O2 M^+=448, $(M+2)^+$=450.

Examples 108-113

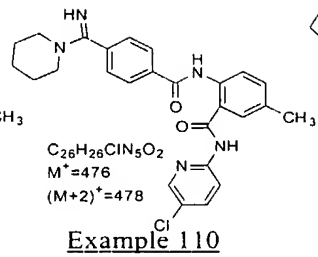
The following compounds were prepared according to the procedure previously described



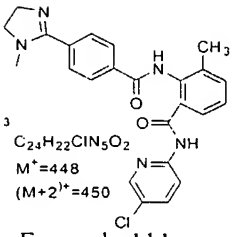
Example 108



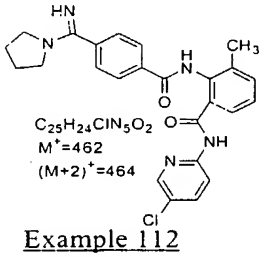
Example 109



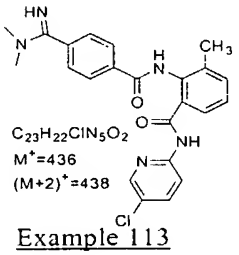
Example 110



Example 111

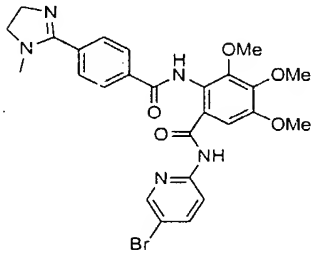


Example 112



Example 113

Example 114



Step 1: To a solution of 3,4,5-trimethoxy-2-nitrobenzoic acid (0.5g, 1.95mmol) in dichloromethane (5ml) was added oxalyl chloride (0.34ml, 3.9mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-bromopyridine (0.81g, 4.7mmol) and pyridine (0.94ml, 11.7mmol) were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide as a solid (790mg, 98%). MS found for C15H14BrN3O6 M^+=412, $(M+2)^+$=414.

Step 2: To a solution of the compound of N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide (790mg, 1.92mmol) in ethyl acetate (5ml) was added tin

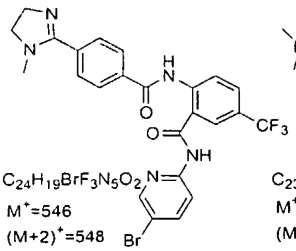
chloride (II) hydrate (1.73g, 7.67mmol). The mixture was stirred under reflux condition for 2 hrs. After filtered by Celite, the filtrate was added 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570mg, 77%). MS found for C15H16BrN3O4 M^+=382, $(M+2)^+$=384.

Step 3: To a solution of the compound of (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570mg, 1.49mmol) in dichloromethane (5ml) was added 3-cyanobenzoly chloride (247mg, 1.49mmol) and pyridine (0.362ml, 4.48mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide as a solid (680mg, 69%). MS found for C23H19BrN4O5 M^+=511, $(M+2)^+$=513.

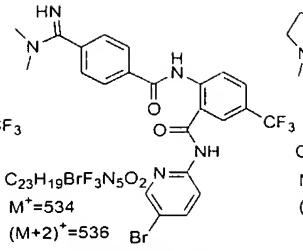
Step 4: To a slotion of the compound of N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide (680mg, 1.33mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.586ml, 6.65mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder (240mg, 32%). MS found for C26H26BrN5O5 M^+=568, $(M+2)^+$=570.

Examples 115-118

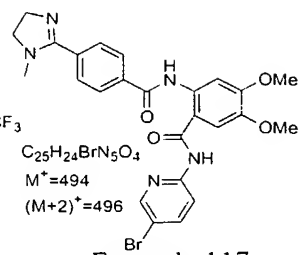
The following compounds were prepared according to the procedure previously described



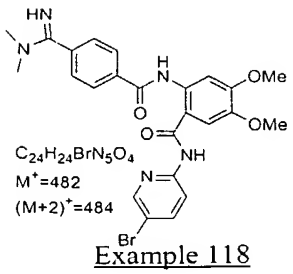
Example 115



Example 116

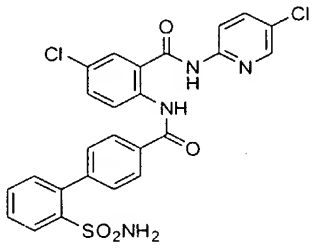


Example 117



Example 118

Example 119



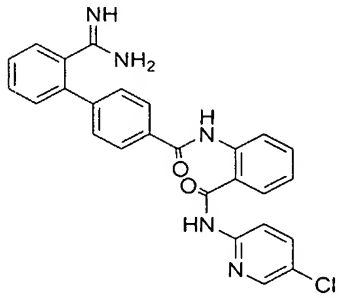
Step 1: To a solution of 4-{2-{[(tert-butyl)amino}sulfonyl}phenyl}benzoic acid (167mg, 0.5mmol) in dichloromethane (5ml) was added oxalyl chloride (0.09ml, 1mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). The compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.17g, 0.6mmol) and pyridine (0.122ml, 1.5mmol) were added to the solution. The mixture was stirred at r.t. overnight. The solvent was evaporated to give (2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide. MS found for C29H26Cl2N4O4S M^+=597, $(M+2)^+$=599.

Step 2: The mixture of the compound of (2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl] carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamideexample 12 (0.5mmol) in trifluoroacetic acid (5ml) was stirred at r.t. for 5hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-(5-chloro(2-pyridyl))(5-chloro-2-{[4-(2-sulfamoylphenyl)-phenyl]carbonylamino}phenyl)-carboxamide as a white powder (68mg, 25%). MS

found for C25H18Cl2N4O4S
M^+=541, $(M+2)^+$=543.

Example 120

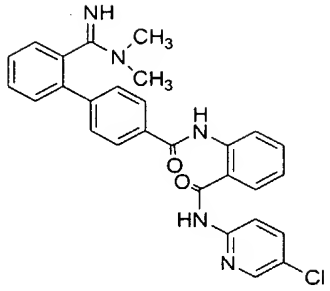
2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]-benzenecarboxamidine



A stream of H_2S (g) was bubbled through a 0 ^{0}C solution of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} [4-(2-cyanophenyl)phenyl]carboxamide (100 mg, 0.22 mmol, 1.0 equiv.) in 9 mL pyridine and 1 mL NEt_3 until saturation. The mixture was stirred at rt for 1 day and evaporated. The resulting residue was treated with MeI (94 mg, 0.663 mmol, 3.0 equiv.) in 10 mL acetone at reflux temperature for 1 hr and concentrated to dryness. The resulting residue was treated with a mixture of NH_4OAc (340 mg, 4.42 mmol, 20 equiv.) in 0.5 mL acetic acid and 2 mL methanol at 50 ^{0}C for 2 days. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzenecarboxamidine (15 mg, 15%). MS found for $C_{26}H_{20}ClN_5O_2$ $(M+H)^+$: 470.

Example 121

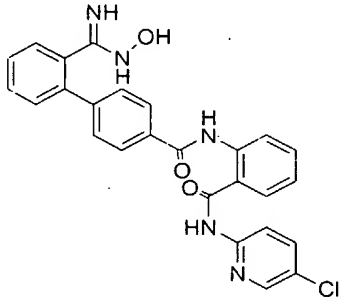
(4-{2-[(dimethylamino)iminomethyl]phenyl}phenyl)-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide



This compound was prepared according to the procedure previously described . MS found for $C_{28}H_{24}ClN_5O_2$ $(M+H)^+$: 498.

Example 122

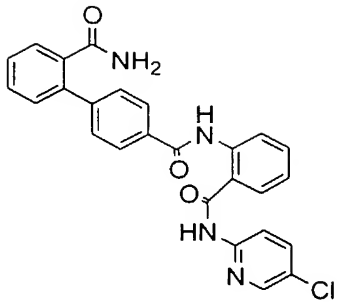
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl)-phenyl]phenyl}carboxamide



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl] carboxamide (14 mg, 0.03 mmol, 1.0 equiv.), hydroxyamine hydrochloride (6.25 mg, 0.09 mmol, 3.0 equiv.) and triethyl amine (0.03 mL, 0.3 mmol, 10.0 equiv.) in ethanol (3 mL) was stirred at rt for 6 days, concentrated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl) phenyl] phenyl}carboxamide (4 mg, 27.5%).
MS found for $C_{26}H_{20}ClN_5O_3$ $(M+H)^+$: 486.

Example 123

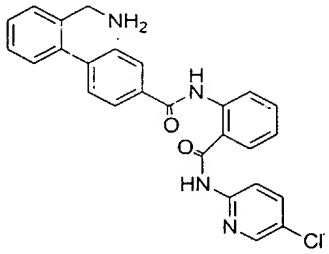
2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzamide



This compound was obtained as oneof the side product in Example 122.
MS found for $C_{26}H_{19}ClN_4O_3$ $(M+H)^+$: 471

Example 124

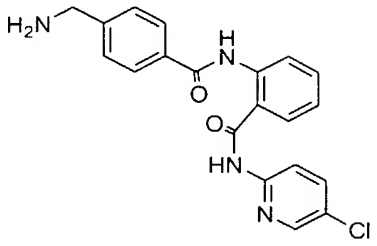
{4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-phenyl}carboxamide



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl] carboxamide (200 mg, 0.442 mmol, 1.0 equiv.), cobalt chloride (86 mg, 0.664 mmol, 1.5 equiv.) and sodium borohydride (50 mg, 1.33 mmol, 3.0 equiv.) in DMF (15 mL) was stirred at 0 ^{0}C to rt for 3 days. The reaction was quenched with ice cubes, diluted with DCM (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave {4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (87 mg, 43%). MS found for $C_{26}H_{21}ClN_4O_2$ $(M+H)^+$: 457.

Example 125

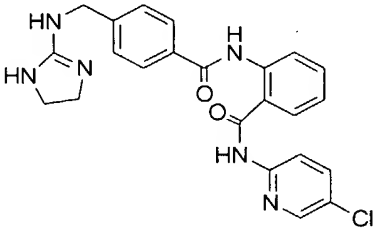
[4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1 g, 2.6 mmol, 1.0 equiv.), cobalt chloride (0.5 g, 3.85 mmol, 1.5 equiv.) and sodium borohydride (0.295 g, 7.8 mmol, 3.0 equiv.) in DMF (20 mL) was stirred at 0 ^{0}C to rt for 2.5 hr. The reaction was quenched with ice cubes, diluted with ethyl acetate (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (320 mg, 30%). MS found for $C_{20}H_{17}ClN_4O_2$ $(M+H)^+$: 381.

Example 126

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]-phenyl}carboxamide

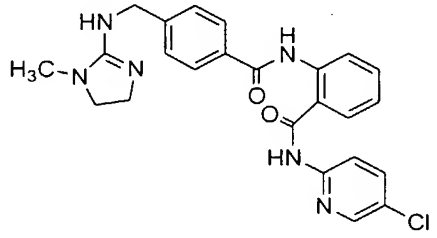


A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (80 mg, 0.21 mmol), 2-methylthio-2-imidazoline hydriodide (77 mg, 0.315 mmol, 1.5 equiv.) and triethyl amine (0.5 mL) in 1 mL DMF was stirred at room temperature overnight, concentrated to dryness and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave N-{2-[N-(5-

chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]phenyl}carboxamide (13.5 mg, 15%). MS found for $C_{23}H_{21}ClN_6O_2$ $(M+H)^+$: 449

Example 127

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl)carboxamide



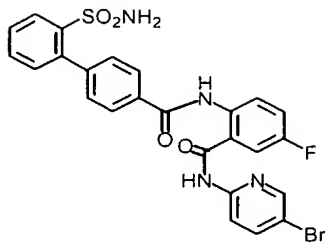
Step 1: To the boiling solution of 2-methylthio-2-imidazoline hydriodide (1 g, 8.4 mmol) in methanol (10 mL) was added MeI (0.78 mL, 12.6 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred at reflux temperature for 1 hr, concentrated and crystallized with ether to give 1-methyl-2-methylthio-2-imidazoline (1.1 g, 100%).

MS found for $C_5H_{10}N_2S$ $(M+H)^+$: 131.

Step 2: A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (74 mg, 0.195 mmol), 1-methyl-2-methylthio-2-imidazoline (25 mg, 0.195 mmol), NEt3 (2 mL) and pyridine (5 mL) was stirred at 80 ^{0}C overnight, concentrated and HPLC (C18 reversed phase)eluting with 0.1% TFA in H2O/CH3CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino]methyl}phenyl)carboxamide (52 mg, 65%). MS found for $C_{24}H_{23}ClN_6O_2$ $(M+H)^+$: 463.

Example 128

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-5-fluorophenylcarboxamide.



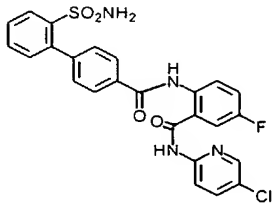
Step 1: A solution of 5-fluoro-2-nitrobenzoic acid (10.0 g, 54 mmol, 1.0 equiv), 2-amino-5-bromopyridine (12.2 g, 1.3 equiv), in 80 mL of pyridine was treated with phosphorous oxychloride (25.3 g, 3.0 equiv) for 30 min. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The volatile was evaporated, and the product was triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (12.5 g, 68%). MS found for $C_{12}H_7BrFN_3O_3$ $(M+H)^+$: 340, 342.

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-flurophenylcarboxamide (2.0 g, 5.88 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_2 2H_2O$ (5.90 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (1.79 g, 98%). MS found for $C_{12}H_9BrFN_3O$ $(M+H)^+$: 310, 312.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.310 g, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (0.430 g, 1.3 equiv), pyridine (2 mL) in 10 mL of dichloromethane was stirred at rt overnight The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was triturated with diethyl ether, and then with chloroform to give N-(5-

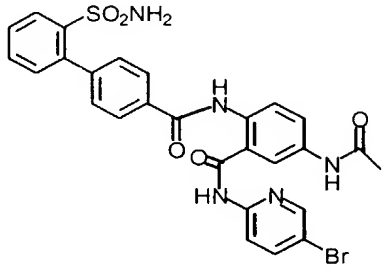
bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)-5-fluorophenylcarboxamide (120 mg, 21%). MS found for $C_{25}H_{18}BrFN_4O_4S$ $(M+H)^+$: 569, 571.

Example 129



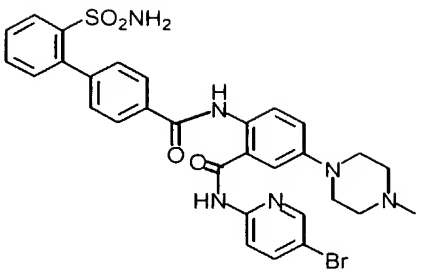
This compound was prepared according to the procedure described in example 2 with the exception of using zinc in acetic acid to reduce nitro-intermediate in step 2. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN. MS found for $C_{25}H_{18}ClFN_4O_4S$ $(M+H)^+$: 525, 527.

Example 130



This compound was prepared according to the procedure described in example 2 with the exception of using 5-acetamido-2-nitrobenzoic acid as the starting material in step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{27}H_{22}BrN_5O_5S$ $(M+H)^+$: 608, 610.

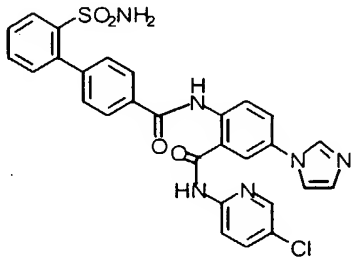
Example 131



This compound is prepared according to the procedure described in example 2 with the exception of the following step 1b performed on the nitro-intermediate from step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{30}H_{29}BrN_6O_4S$ $(M+H)^+$: 649, 651.

Step 1b: A mixture of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (0.68 g, 2 mmol, 1.0 equiv), N-methylpiperazine (0.60 g, 3 equiv), and Cs_2CO_3 (1.30 g, 2 equiv) in 5 mL of dimethylformamide was stirred at 90°C overnight. Ethyl acetate was added and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered, evaporated, purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-(4-N-methylpiperazine)phenylcarboxamide (0.54g, 65%). MS found for $C_{17}H_{18}BrN_5O_3$ $(M+H)^+$: 419, 421.

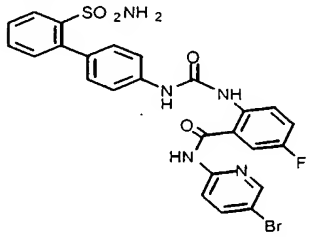
Example 132



This compound was prepared according to the procedure described in example 5. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{28}H_{21}ClN_6O_4S$ $(M+H)^+$: 573, 575.

Example 133

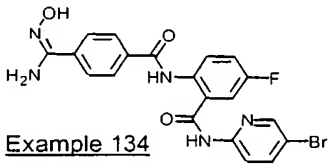
N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide.



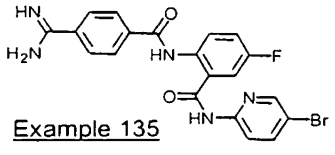
Step 3: A mixture of 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.180 g, 1.2 equiv), N,N'-disuccinimidyl carbonate (0.154 g, 1.2 equiv), 4-methylmorpholine (0.5 mL) in 10 mL of acetonitrile was stirred at rt for 30 min. N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.155 g, 0.5 mmol, 1.0 equiv) was added and the solution was stirred at rt for 3 hrs. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylaminocarbonylamino)-5-fluorophenylcarboxamide (0.053 g, 18%). MS found for $C_{25}H_{19}BrFN_5O_4S$ $(M+H)^+$: 584, 586.

Examples 134-135

N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide.



Example 134



Example 135

Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)5-fluorophenylcarboxamide (1.24 g, 4 mmol, 1.0 equiv), 4-cyano benzoyl chloride (0.792 g, equiv), and pyridine

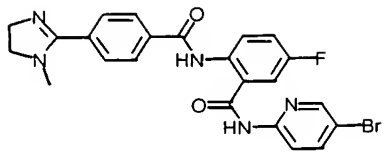
(3 mL) in 15 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.14 g, 65%). MS found for $C_{20}H_{12}BrFN_4O_2$ $(M+H)^+$: 439, 441.

Step 2: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.12 g, 2.56 mmol, 1.0 equiv), hydroxylamine-HCl (0.213 g, 1.2 equiv), and triethylamine (1 mL) in 15 mL of ethyl alcohol was stirred at 50°C overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (compound Example 194) (0.84 g, 70%). One third of this material was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to yield 0.20 grams (71%). MS found for $C_{20}H_{15}BrFN_5O_3$ $(M+H)^+$: 472, 474.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (0.56 g, 1.19 mmol, 1.0 equiv) and zinc dust (0.39 g, 5.0 equiv), in 10 mL of acetic acid was stirred at rt for 45 min. The volatile was filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenyl-carboxamide (compound Example 195) (0.24 g, 44%).
MS found for $C_{20}H_{15}BrFN_5O_2$ $(M+H)^+$: 456, 458.

Example 136

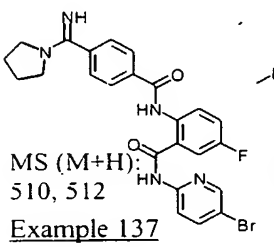
N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide.



Step 1: A stream of HCl(g) was bubbled through a 0^0C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.0 g, 2.3 mmol) in 30 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. One-fifth of the resulting residue was treated with (2-aminoethyl)methylamine (0.10 g) in 10 ml methanol at rt overnight. The solvent was removed at reduced pressure and the crude product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide (0.082 g, 37%). MS found for $C_{23}H_{19}BrFN_5O_2$ $(M+H)^+$: 496, 498.

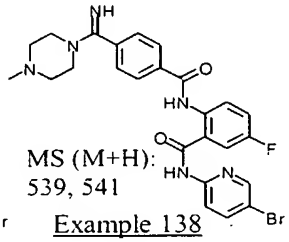
Examples 137-198

The following compounds were prepared generally according to the procedure described in Example 196.



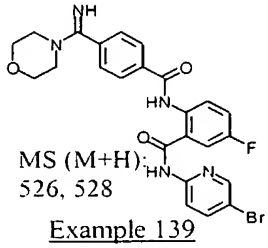
MS (M+H): 510, 512

Example 137



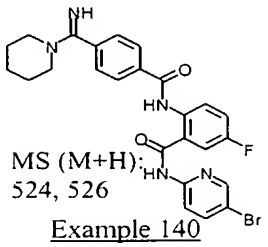
MS (M+H): 539, 541

Example 138



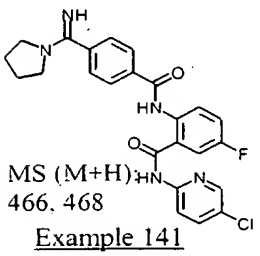
MS (M+H): 526, 528

Example 139



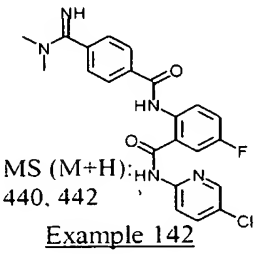
MS (M+H): 524, 526

Example 140



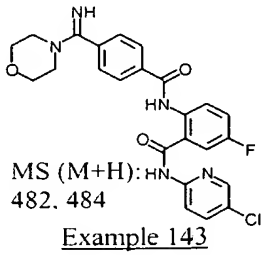
MS (M+H): 466, 468

Example 141



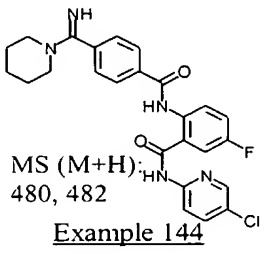
MS (M+H): 440, 442

Example 142



MS (M+H): 482, 484

Example 143



MS (M+H): 480, 482

Example 144